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Health and Environmental Effects Profile for Methoxychlor

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16. ABSTRACT

The Health and Environmental Effects Profile for methoxychlor was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Methoxychlor has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for methoxychlor is 7 mg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a relase as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR METHOXYCHLOR

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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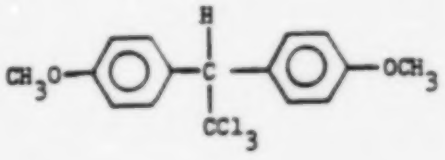
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BOD	Biochemical oxygen demand
BUN	Blood urea nitrogen
bw	Body weight
CNS	Central nervous system
DNA	Deoxyribonucleic acid
GI	Gastrointestinal
GLC	Gas-liquid chromatography
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MS	Mass spectra
NOAEL	No-observed-adverse-effect level
NMR	Nuclear magnetic resonance
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TLC	Thin-layer chromatography
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE, CAS NUMBER AND RTECS NUMBER

Methoxychlor is also known as 2,2-bis(4-methoxyphenyl)-1,1,1-trichloroethane, 2,2-di-α-anisyl-1,1,1-trichloroethane, DMDT, methoxy-DDT, and Marlate (trade name). Its structure, molecular weight and empirical formula are given below:



Empirical formula: $C_{16}H_{15}Cl_3O_2$

Molecular weight: 345.65

The Chemical Abstracts Service (CAS) Registry number for methoxychlor is 72-43-5. The Registry of Toxic Effects of Chemical Substances (RTECS) number is KJ3675000.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Methoxychlor is a pale yellow crystalline solid that is used as an insecticide (Windholz, 1976; Hawley, 1977). Some of the physical properties of methoxychlor are listed below:

Log octanol/water partition coefficient	3.05 (Coats et al., 1979) 3.31 (Kapoor et al., 1973) 3.68 (Kapoor et al., 1970) 4.30 (Fujita, n.d.) 4.68 (Hansch and Leo, 1979)

Solubility: (Brooks, 1947, unless otherwise stated)

Solvent	Solubility (g/100 g at 22°C)
Acetone	60
Methylene chloride	60
Dichlorobenzene	40
Cyclohexanone	50
Xylene	40
Methylated naphthalenes	35
Carbon tetrachloride	16
Methanol	<5
Odorless kerosene	2
Water (Richardson and Miller, 1960)	0.1 mg/ℓ at 25°C
Water (Zepp et al., 1976)	0.12 mg/ℓ at 25°C
Natural seawater (salt content = 25 ppt) (Liu and Lee, 1975)	0.05 mg/ℓ at 20°C

Lamoureux and Fell (1980), Mitchell et al. (1978), and West et al. (1982) have identified 38 of the ~50 impurities found in technical methoxychlor. The actual concentrations of the impurities vary from lot to lot and it is possible that some of the impurities found by these authors will not be present in all methoxychlor lots. Technical methoxychlor contains from 88-90% of the p,p'-isomer (Martin and Worthing, 1977; West et al., 1982).

1.3. PRODUCTION DATA

Recent data detailing methoxychlor production volumes were not found in the available literature. In 1975, three companies in the United States produced 2.5 million kg of the 5.5 million kg total United States production (USITC, 1977). The major producers in 1984 are listed in Table 1-1. Chemical Formulators, Inc., had a 1975 production capacity of 1.13 million kg/year (2.5 million pounds/year), while DuPont had a 1.36 million kg/year (3 million pounds/year) capacity (Ayers and Johnson, 1976). Methoxychlor is made by the condensation of anisole (methoxybenzene) and chloral (trichloroacetaldehyde), using sulfuric acid as the catalyst (Schneller and Smith, 1949).

TABLE 1-1

Methoxychlor Producers and Locations*

Producer	Location
Kincaid Enterprises, Inc.	Fillmore, CA Nitro, WV
Lee Pharmaceuticals Lee Chemicals Co. Div.	Fillmore, CA

*Source: SRI International, 1984

1.4. USE DATA

Ayers and Johnson (1976) reported that the total 1974 domestic consumption by all markets was 1.5 million kg (3.3 million pounds). Of this, 0.454 million kg were used for agricultural crop markets (alfalfa, deciduous fruits/nuts, soybeans, vegetables), and 1.09 million kg was used in non-agricultural crop markets (forests, home and garden, ornamentals, livestock/poultry, commercial, household and industrial establishments). In 1976, 0.652 million kg (1.4 million lb) were used for agricultural crop markets (principally alfalfa), and 1.4 million kg (2.4 million lb) were used as a livestock insecticide (USDA, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. ATMOSPHERIC FATE AND TRANSPORT

No reports were found in the available literature describing the vapor-phase chemistry of methoxychlor. Ginsburg (1953) reported that a dry, thin film of methoxychlor, when exposed to sunlight, "readily decomposed". After 12 days, 40% of the original 10 mg sample had disappeared, but 91.4% of a 5 mg sample disappeared after the same time. Because the total amount lost in both 12-day experiments was the same, it seems likely that a mechanism other than photolysis was operating. In addition, no dark controls were run. Therefore, methoxychlor disappearance may be from volatilization rather than photolysis. MacNeil et al. (1972) also exposed methoxychlor on a Pyrex plate to sunlight. After 2 months, 100 mg underwent a virtually complete breakdown. Analysis by MS of the nonpolar fraction from TLC showed trace amounts of 1,1-bis(p-methoxyphenyl)-2,2-dichloroethylene (DMDE). This compound has been found in technical methoxychlor (see Section 1.2.), although Zepp et al. (1976) also reported the presence of DMDE after the photolysis of methoxychlor in aerated solvents.

2.2. FATE AND TRANSPORT OF METHOXYCHLOR IN WATER

Wolfe et al. (1977) studied the chemistry of methoxychlor and DDT in water. The authors conducted a detailed hydrolysis study at elevated temperatures and then extrapolated the data to environmentally realistic temperatures. Methoxychlor disappearance followed first-order kinetics for the pH range 3-9. These data show that at 27°C, the first-order rate constant will be 2.2×10^{-8} sec^{-1} at pH 7. This corresponds to a half-life of 367 days. Anisoin and anisil are the major hydrolysis products and do not result from the same mechanism by which DDT degrades. Unlike methoxychlor, hydrolysis of DDT results in an environmentally persistent compound. When

methoxychlor was hydrolyzed in two natural river waters and compared with the distilled water data, no detectable changes in the rate were seen; Wolfe et al. (1976) noted that degradation of methoxychlor in the environment was too fast to be accounted for by hydrolysis and another process (probably biodegradation) is dominant.

Several investigators have studied the photolysis of methoxychlor. Zepp et al. (1976) and Wolfe et al. (1976) reported that the major photoproduct of methoxychlor in oxygenated heptane was 4,4'-dimethoxybenzo-phenone (MDCO) with 2,2-bis(p-methoxyphenyl)-1,1-dichloroethane (DMDD), DMDE and p-methoxy-phenol as minor products. Photolysis of water-insoluble organics such as methoxychlor in hydrocarbon solvents is environmentally significant, since it has been reported that these compounds concentrate in organic surface films (Seba and Corcoran, 1969).

Zepp et al. (1976) also photolyzed methoxychlor in air saturated water with >280 nm light. After ~10% conversion of methoxychlor, DMDE accounted for 60% of the products, but the yield decreased thereafter because of subsequent DMDE photolysis. p-Anisaldehyde was also present, but no MDCO was detected (as was the case with heptane). When air-saturated, acetonitrile-water was used as the solvent, DMDE was formed in 60% yield, but dropped to a 20% yield in degassed acetonitrile-water. The addition of a free radical scavenger resulted in a sharp decrease in the DMDE yield and gave rise to DMDD formation. These results suggested homolysis of a carbon-chlorine bond to form a free radical intermediate, a photoprocess identical to that of DDT.

The results from photolysis in distilled water indicated that the reaction was slow; however, photolysis in sterilized natural waters was much faster (Table 2-1). GLC traces of the reaction products had a peak with the same retention time as DMDE. When methoxychlor was added to humic acid in

TABLE 2-1

Half-lives for Photodecomposition of Methoxychlor (40 ppb) by Sunlight in Various River Waters[a,b]

Water	pH	Photolysis Half-life[c] (hours)
Distilled	6.3	>300
Swannee River	4.7	2.2
Tombigbee River	7.6	5.4
Alabama River	7.7	2.9
Withlacoochee River	8.2	ND[d]
South Georgia stream[e]	7.2	ND[d]
20 ppm of "humic acid" in distilled water[f]	5.2	7.3

[a]Source: Wolfe et al., 1976

[b]Solution in sealed quartz cells exposed to midday sunlight in May, latitude 34°N.

[c]Calculated assuming first-order kinetics, expressed as hours of midday sunlight.

[d]No detectable photolysis after 2 hours of exposure.

[e]Collected near Thomasville, GA

[f]Aldrich Chemical Company humic acid

distilled water, a half-life roughly equivalent to that of natural waters was noted. The process involving absorption of light by materials present in natural water followed by decomposition of the pesticide is called indirect or sensitized photolysis; however, the exact mechanism for this process is not known. In the case of methoxychlor, energy transfer photosensitization was not occurring, since the triplet state energy for methoxychlor (80 kcal/mol) is higher than the absorbing substances in the natural waters (and humic acid). Singlet oxygen was also precluded as an important reactant. Zepp et al. (1976) suggested that an exciplex mechanism similar to the amine-induced photolysis of DDT was possible, as was methoxychlor decomposition from free radicals generated by photolysis of materials present in the natural waters.

DMDE, the major photoproduct of methoxychlor, on photolysis gives cis- and trans-1-(2-chloro-4-methoxyphenyl)-1-(4-methoxyphenyl)-2-chloroethylene (photo-DME), as well as DMCO and 1,1-bis(4-methoxyphenyl)-2-chloroethylene (DMDU) (Zepp et al., 1976). These authors also suggested that, given the low water solubility of these compounds, methoxychlor and its photoproducts would likely sorb to sediments and be unavailable for photolysis. Oliver et al. (1979) reported that sediments in water did slow the photolysis rate of methoxychlor, although they determined that the major effect in their system was light attenuation rather than sorption.

Based on data from DDT, methoxychlor is expected to volatilize from water, although little data are available in the form of direct measurements. Mackay et al. (1980) noted that, along with polychlorinated biphenyls, DDT, malathion, and parathion, methoxychlor has a surprisingly high activity coefficient. This indicates that it will volatilize from water more rapidly than would be expected based on its water solubility,

vapor pressure and lipid solubility. Strachan et al. (1980) and Strachan and Huneault (1979) measured the concentration of some organochlorine compounds, including methoxychlor, in rain and snow over the Great Lakes during 1976-1977. That methoxychlor is present in rain supports the laboratory observations that methoxychlor volatilizes from soil and water. The average concentration was 9 ng/ℓ in rain over industrialized areas, while more remote areas averaged 5 ng/ℓ.

Karickhoff et al. (1979) reported that methoxychlor sorption to sediments is directly related to the organic carbon content for a given particle size. The K_{oc} values reported by Karickhoff et al. (1979) varied between 82,000 and 93,000, with coarse silt and clay having the lowest values, and medium and fine silts the highest. Brockway et al. (1979) studied methoxychlor dissipation in a flowthrough ecosystem. The system was allowed to equilibrate for 73 days; then the methoxychlor was introduced and allowed to dissipate over 17 weeks. Of the 194 µg of methoxychlor introduced, 17 µg were exported in the effluent, ~1 µg was present on wall growth, ~6 µg were present in the alga, and ~7 µg in the sediment. The total found at the termination plus that exported represents 16% of the total added; 84% decomposed or became bound to materials.

The Canada Centre for Inland Water (CCIW, 1973) studied methoxychlor in Lakes Erie and Ontario and reported that methoxychlor did translocate into the water, but the input route was not identified. They reported finding trace amounts of methoxychlor in some species of fish and plankton, but there were no detectable amounts in the water or sediments (limit of detection was 0.01 µg/ℓ), although this observation may be the result of limited use of methoxychlor. Bradshaw et al. (1972) found methoxychlor residues in water samples from the tributaries of Utah Lake in Utah, but it

was never detected in the Jordan River outlet. Methoxychlor levels in the water varied with season; the highest concentrations were in late spring but methoxychlor was also present in late fall. No sediments were sampled for methoxychlor; sediment is a possible sink for waterborne pesticides. Wallner et al. (1969) found that 1 µg/kg of methoxychlor persisted in bottom silt from spring to fall after the aerial spraying of methoxychlor. Fredeen et al. (1975) reported that 9 days after treatment of the Saskatchewan River (for blackfly control), residues of 0.05-0.1 mg/kg were present in sand samples taken 22 km downstream. No residues were detectable from treatment made the previous year, although it is not clear whether this indicated degradation or transfer and subsequent dilution downstream. The authors' data demonstrated that ~50% of the total methoxychlor found in the river water samples was bound to the sediments. Luczak (1969) measured methoxychlor decomposition in slightly polluted surface waters and reported a 90% decrease after 169 days (initial concentration was 1.5 mg/ℓ); however, the abstract of this paper does not mention whether biodegradation was the primary means of disappearance.

2.3. FATE AND TRANSPORT IN SOIL

Methoxychlor, once in the soil, can be removed by hydrolysis, photolysis, volatilization, leaching or microbial degradation. No reports were found in the available literature concerning chemical processes (i.e., photolysis or hydrolysis) on the soil surface, although it seems likely that both processes will occur to some extent. Photolysis will occur only on the soil surface and, therefore, probably will not be a dominant process. The likelihood and extent of hydrolysis will be dependent on soil moisture. Data concerning methoxychlor volatilization from soil are also sparse. In a model terrestrial ecosystem, Metcalf et al. (1979) noted a significant loss

of methoxychlor because of volatilization. Unfortunately, vermiculite was used instead of soil, and it seems likely that sorption onto soil will be significantly stronger than onto vermiculite. Hunt and Sacho (1969) reported DDT and methoxychlor soil residues remaining after elm tree treatment. Methoxychlor was applied at 10.7, 11.2 and 10.6 pounds/acre in 1961, 1962 and 1963, respectively, the last treatment being in April 1963. Their data are presented in Table 2-2. Both DDT and methoxychlor remained in the top 6 inches of soil, the majority of each remaining in the top inch. Methoxychlor disappearance seems to be more rapid.

Fogel et al. (1982) exposed soil treated with 1000 ppm methoxychlor to varied conditions. Soils were initially incubated for 100 days under either aerobic, anaerobic or denitrifying conditions. At the end of this period, the soils exposed to anaerobic and denitrifying conditions were flushed with air and inoculated with 0.1 g of soil previously incubated with methoxychlor under aerobic conditions. Evolution of $^{14}CO_2$ was monitored after the changeover to aerobic conditions. Changing from anaerobic to aerobic conditions produced a 70- and 15-fold increase in $^{14}CO_2$ evolution for duplicate flasks when compared with a control that had been maintained under aerobic conditions only. Gas chromatographic analysis of the soils showed virtually no removal of methoxychlor under aerobic conditions, but significant removal under denitrifying and anaerobic conditions, even though no $^{14}CH_4$ or $^{14}CO_2$ was evolved. Sterile controls showed no methoxychlor removal. The authors speculated that methoxychlor is transformed under anaerobic or denitrifying conditions to dechlorinated species that readily degrade under aerobic conditions.

Few studies in the literature discuss the microbial degradation of methoxychlor in soil. In laboratory experiments, Castro and Yoshida (1971)

TABLE 2-2

Insecticides in Soil After Elm Tree Treatment with DDT or Methoxychlor[a,b]

Date Sampled	Depth (inches)	Residues (mg/kg dry weight) DDT	Methoxychlor	DDE	DDD
Area A					
August 1963	0-1	13.8	8.6	4.2	1.3
	1-3	3.5	1.4	1.8	0.4
	3-6	0.7	0.9	0.7	0.1
	0-6	5.4	1.8	1.2	0.5
	0-3	5.4	3.0	2.5	0.5
April 1964	0-3	6.3	1.8	2.0	0.9
Area B					
April 1964	0-3	8.6	1.1	2.5	1.0

[a]Source: Gardner and Bailey, 1975

[b]DDT was applied in 1960 and 1961 at 12.9 lb/acre and 11.7 lb/acre, respectively. All spraying was done in late March or early April.

found that in three of four flooded soils, 27 ppm of methoxychlor disappeared within 3 months, while in unflooded (water content was 80% of maximum holding capacity) soils the same amount of methoxychlor found in the soils varied between 11 and 19 ppm. These investigators also found that under flooded conditions, the higher the organic matter content of the soil, the faster the degradation. Interpolating from the graphs, times for 50% disappearance were 10, 24, 30 and 45 days at organic matter concentrations of 4.4, 3.2, 2.0 and 1.5, respectively. The times for 50% disappearance in upland soils were >90 days; however, sterile controls were not mentioned in the text so the extent of abiotic methoxychlor removal cannot be assessed. Subba-Rao and Alexander (1977), using BOD bottles and silt loam soil as an inoculum, reported little O_2 uptake by methoxychlor after 30 days.

Pure culture studies provide little meaningful information about the extent and rate of biodegradation of chemicals in the environment, but they do define possible metabolic pathways. Published data regarding methoxychlor metabolism by pure culture are also sparse. Mendel et al. (1967) reported that aerobic and anaerobic cultures of Enterobactea aerogenes contained two methoxychlor metabolites. One anaerobic culture contained DMDE (80% of the initial methoxychlor), while another anaerobic culture contained DMDD (30% of the initial methoxychlor). DMDE was also found in one of five aerobic cultures (12% of the initial methoxychlor). Baarschers et al. (1982) restudied this bacterium and found 2,2-bis(p-methoxyphenyl)-1,1-dichloroethane also present. Of four bacterial cultures screened for the removal of methoxychlor, Paris et al. (1975) found only one, Flavobacterium harrisonii, able to degrade methoxychlor within 216 hours. DMDE was the only product identified.

3. EXPOSURE

Methoxychlor is used as an insecticide to control household and garden pests. It is also used to alleviate problems of insect infestations in rangeland and is introduced directly into streams to kill blackfly larvae before they can emerge as adults. Methoxychlor residues, therefore, can be expected to be present in a number of media. In this section, the levels of methoxychlor in air, water and aquatic organisms, sediments and soils, household dusts, foods, and human blood and milk are presented. In addition, human exposure and intake of methoxychlor from various routes of entry are evaluated.

3.1. AIR

Methoxychlor can enter the atmosphere, as DDT does, by way of volatilization from water, soil and plant surfaces after application. Some methoxychlor in the atmosphere may originate from wind erosion of methoxychlor-treated soil. Few monitoring data are available regarding methoxychlor levels in the ambient air, although the lack of data may well be due to limited use of this compound compared with DDT. Warnick and Eldredge (1972) monitored pesticide levels in Utah air in 1970. Although a few other pesticides were found to be present, no methoxychlor could be detected (detection limit 1 ng/m^3). Despite this, the presence of methoxychlor in air over the Great Lakes can be indirectly concluded from its presence in snow and rainwater (Strachan et al., 1980).

Until more data regarding the ambient air concentrations of methoxychlor are available, the amount of human exposure to this insecticide through inhalation is difficult to determine.

3.2. WATER AND AQUATIC ORGANISMS

Methoxychlor levels have been monitored in a variety of aquatic media as shown in Table 3-1. Although low levels of methoxychlor in surface waters

TABLE 3-1

Methoxychlor Residue Levels in Aquatic Media

Origin and Media	Year Sampled	Percent with Positive Level	Average Concentration;[a] ppb in positive samples	Detection Limit (ppb)	Reference
Galveston Bay, TX, water	1964	11	<1.0	1.0	Casper, 1967
Lower Mississippi River:					
East Jefferson Water Works	1970	0	ND	<0.1	Brodtmann, 1976
West Jefferson Water Works	1970	0	ND	<0.1	Brodtmann, 1976
Lake Michigan:					
Lake water	1971	100	0.016 (0.003-0.03)	0.001	Schacht, 1974
Lake water	1972	100	0.048 (0.023-0.089)	0.001	Schacht, 1974
Sewage Treatment Plant at North Shore Sanitary District, Chicago:					
Water	1971	100	0.036 (ND-0.106)	0.001	Schacht, 1974
Water	1972	100	0.035 (0.021-0.060)	0.001	Schacht, 1974
North Saskatchewan River following injection of methoxychlor:					
Water	1972	100	150.0 (140-160)	10	Fredeen et al., 1975

TABLE 3-1 (cont.)

Origin and Media	Year Sampled	Percent with Positive Level	Average Concentration;[a] ppb in positive samples	Detection Limit (ppb)	Reference
Habitant Creek Watershed, Nova Scotia:					
Drainage ditch water during thunderstorm	1972-1973	NA[b]	0.04	NR	Burns et al., 1975
Drainage ditch water 3 days after thunderstorm	1972-1973	0	ND	NR	Burns et al., 1975
Creek water:					
Spring	1972-1973	NA[b]	0.01	NR	Burns et al., 1975
Summer	1972-1973	NA[b]	ND	NR	Burns et al., 1975
Fall	1972-1973	NA[b]	0.02	NR	Burns et al., 1975
Winter	1972-1973	NA[b]	ND	NR	Burns et al., 1975
Artesian well near creek	1972-1973	NA[b]	ND	NR	Burns et al., 1975
Holding pond near creek	1972-1973	NA[b]	0.06	NR	Burns et al., 1975
Lake Superior water	NR	0	ND	0.01	Glass et al., 1977
Great Lakes and inland:					
Snow	1975-1976	NR	0.002	0.001	Strachan et al., 1980
Rain	1976-1977	NR	0.007 (0.001-0.013)	0.001	Strachan et al., 1980
Royal Botanical Gardens, Hamilton, Ontario:					
Pond water	NR	0	ND	NR	Kalas et al., 1950
Lake Nakuru, Kenya:					
Water	1975	0	ND	NR	Greichus et al., 1978

TABLE 3-1 (cont.)

Origin and Media	Year Sampled	Percent with Positive Level	Average Concentration;[a] ppb in positive samples	Detection Limit (ppb)	Reference
James River near Windmill Point, VA: Water	1976	NR	<0.008	0.008	Saleh et al., 1978
Canal water near Snake River, ID	1980	NR	(1.4-<0.1)	NR	Stoltz and Pollock, 1982
Niagara River water at Lake Ontario	1980-1981	7	0.1 ppt	0.1 ppt	Kuntz and Warry, 1983
Niagara River suspended sediment at Lake Ontario	1979-1981	51	7	1	Kuntz and Warry, 1983
Niagara River water near Love Canal	1981	NR	0.0010	0.0001	Maguire et al., 1983
Niagara River suspended solids near Love Canal	1981	NR	0.015 mg/kg	0.001 mg/kg	Maguire et al., 1983
Lake Michigan sediments (top 3 cm)	1975	0	ND	NR	Frank et al., 1981
New Jersey groundwater (408 well survey)	NR	NR	detected, not quantified	NR	Greenberg et al., 1982

TABLE 3-1 (cont.)

Origin and Media	Year Sampled	Percent with Positive Level	Average Concentration;[a] ppb in positive samples	Detection Limit (ppb)	Reference
California groundwater San Joaquin Merced Fresno Santa Barbara Kern	NR	NR	detected, not quantified	NR	Maddy et al., 1982
Waste sewage sludge disposal site, Colorado	NR	NR	ND	NR	Baxter et al., 1983

[a]Values in parentheses indicate the range of concentration.

[b]Multiple analysis results not available.

ND=not detected

NR=not reported

have been reported, levels in drinking water above the detection limit were not found in the available literature. Even the water of an artesian well located close to the site of methoxychlor application failed to show any methoxychlor concentration (Burns et al., 1975).

While many aquatic organisms do not accumulate methoxychlor from water, some species do. In general, fish and homeotherms appear to metabolize methoxychlor fairly rapidly and do not accumulate this compound (Gardner and Bailey, 1975). Aquatic organisms that live in the sediment, filter feeders, and terrestrial organisms may accumulate methoxychlor. For example, the water snail, Physa, has an accumulation factor of 2600 for methoxychlor (Reinbold et al., 1971). Similarly, Daphnia magna and soft-shell clams have concentration factors of 2200 and 1500, respectively (Reinbold et al., 1971; Butler, 1971). Aquatic organisms, therefore, could become critical species that need careful monitoring. The methoxychlor levels in aquatic organisms that may be consumed by humans are given in Table 3-2. As expected, some mussels and oysters have been shown to contain methoxychlor. Fish, with the exception of a few species, do not contain any detectable level of methoxychlor, even in species taken from contaminated waters. A summary of STORET Data Base information is presented in Table 3-3.

3.3. SEDIMENTS AND SOILS

Methoxychlor, when applied to orchards and dairy areas (Moubry et al., 1968), could result in the contamination of soils. Methoxychlor can be moderately persistent, and detectable residues may remain in some soils for 14 months after a single application (Gardner and Bailey, 1975). Although the contamination of soils may not result in direct exposure of humans to methoxychlor, it may lead to indirect exposure. For example, run-off from

TABLE 3-2

Methoxychlor Residue Levels in Aquatic Organisms

Origin and Species	Year Sampled	Percent with Positive Level	Average Concentration;[a] ppm in positive sample	Detection Limit (ppm)	Reference
Galveston Bay, TX: Oyster	1964	0	ND	<0.01	Casper, 1967
Gulf of Mexico and South Atlantic: Oyster	1964-1966	4.5	<0.01	0.01	Buggs et al., 1967
U.S. Estuary: Habitats (oyster, mussel, clam)	1965-1972	0	ND	0.005	Butler, 1973
Red Cedar River, MI: Mussels	1966	NR	(0.09-0.18)	NR	Bedford et al., 1968
California Bay and Estuary: Habitats (oyster, mussel, clam, crab, prawn, fish)	1966	0	ND	0.01	Modin, 1969
California Coast: Whales	1968-1969	0	ND	<0.01	Wolman and Wilson, 1970
Lake St. Clair: Fish	1968-1976	0	ND	0.005	Frank et al., 1978
Lake Erie: Fish	1968-1976	0	ND	0.005	Frank et al., 1978

TABLE 3-2 (cont.)

Origin and Species	Year Sampled	Percent with Positive Level	Average Concentration;[a] ppm in positive sample	Detection Limit (ppm)	Reference
Northeastern Pacific Ocean:					
Fish	1969-1970	0	ND	<0.01	Duke and Wilson, 1971
Lake Michigan:					
Yellow perch	1971	0	ND	10^{-4}	Schacht, 1974
Chub	1971	0	ND	10^{-4}	Schacht, 1974
Carp	1971	46.4	(<0.1-0.1)	10^{-4}	Schacht, 1974
Coho salmon	1971	3	0.1	10^{-4}	Schacht, 1974
Alewife	1971	0	ND	10^{-4}	Schacht, 1974
U.S. Estuary:					
Fish	1972-1976	0	ND	0.03	Butler and Schulzmann, 1978
Athanasca River: (after treatment)					
Rainbow trout	1976	100	(0.23-1.75)	0.00002	Lockhart et al., 1977
North Saskatchewan River immediately following injection of methoxychlor:					
Gold eye	1972	66	(0.02-1.5)[b]	<0.01	Fredeen et al., 1975
Sucker	1972	0	ND	<0.01	Fredeen et al., 1975
Pickeral and sauger	1972	0	ND	<0.01	Fredeen et al., 1975
Northern pike	1972	0	ND	<0.01	Fredeen et al., 1975
Mussel	1972	0	ND	<0.01	Fredeen et al., 1975

TABLE 3-2 (cont.)

Origin and Species	Year Sampled	Percent with Positive Level	Average Concentration;[a] ppm in positive sample	Detection Limit (ppm)	Reference
Utah Lake (after treatment)					
Carp	1970	100[c]	0.59	NR	Bradshaw et al., 1971
Lake Superior:					
Upper lake fish	NR	0	ND	0.002	Glass et al., 1977
Offshore fish	NR	100	0.05	0.002	Glass et al., 1977
Lake Nakuru, Kenya:					
Fish	1975	0	ND	NR	Greichus et al., 1978
U.S. Estuary:					
Mollusks	1977	0	ND	0.03	Butler et al., 1978
Lake Huron:					
Upper lake fish	NR	0	ND	0.002	Glass et al., 1977
Offshore fish	NR	100	0.05	0.002	Glass et al., 1977

[a]Values in parentheses indicate the range in concentration
[b]The level of methoxychlor was below the detection limit after ~2.5 months
[c]Two fish were analyzed
ND = Not detected
NR = Not reported

TABLE 3-3

STORET Summary

Sample type	Number of Samples	Concentration		
		Maximum	Minimum	Mean
Whole water	21,607	1000 µg/ℓ	0.0 µg/ℓ	5.58 µg/ℓ
Bottom deposits (dry weight)	6,731	8000 µg/kg	0.0 µg/kg	15.7 µg/kg
Fish (whole)	39,482	590 µg/kg	0.0 µg/kg	24.9 µg/kg
Fish tissue (wet weight)	2,654	10 µg/kg	0.0 µg/kg	0.037 µg/kg
Shell fish (dry weight)	5,026	100 µg/kg	5.0 µg/kg	7.71 µg/kg

soils may contaminate surface waters, and farm products touching contaminated soils may contain residues. Methoxychlor originating in water either from direct application or from runoff is adsorbed relatively strongly in suspended solids and sediments or aquatic bodies. The particulate matter acts as a sink for methoxychlor by removing a portion of the compound from water. Sediments, therefore, are the prime critical pool to consider in any discussion of the impact of methoxychlor upon aquatic fauna.

The levels of methoxychlor monitored in a few soils and aquatic sediments are given in Tables 3-4 and 3-5, respectively. It appears from these tables that methoxychlor is more prevalent in aquatic bottom sediments than in soils.

3.4. HOUSEHOLD DUSTS

The origin of methoxychlor in household dust may be its application as a pest control agent inside residences, particularly in tropical areas. In the United States, it is rarely used for this purpose. Household dust in Utah was analyzed in 1970 by Warnick and Eldredge (1972); no detectable level of methoxychlor were found. The household dust from a control group of residences in Colorado in 1968, however, showed moderately high levels of methoxychlor (Table 3-6).

Places outside the United States where methoxychlor is frequently used for pest control have had very high levels reported (Davies, 1975). The interior household dust showed two orders of magnitude higher concentrations than the exterior dust and soil in one study (Davies, 1975). In the United States, moderately high methoxychlor levels have been reported in the household dust of farmers and pesticide formulators (samples consisted of 1 month's sweepings collected in a vacuum cleaner, taken over a 12-month period) (Table 3-6).

TABLE 3-4

Methoxychlor Residue Levels in Soils

Origin of Soil	Year Sampled	Percent with Positive Level	Concentration* (ppm)	Detection Limit (ppm)	Reference
Thirty-four sites in Wisconsin	1909-1911	0	ND	0.001	Frazier et al., 1970
Sixteen southwestern Ontario farms	1964, 1966, and 1969	0	ND	0.01 (1964) 0.001 (1966 and 1969)	Harris and Sans, 1971
Wisconsin and 8 other states west of the Mississippi River	1967	0	ND	0.01	Trautmann et al., 1968
Major agricultural soils in the United States	1968-1973	0	ND	<0.03	Carey, 1979
Cropland soils from 43 states	1969	<0.1	1 out of 1729 soils: 0.28	0.01	Wiersma et al., 1972
Cropland soils from 35 states	1970	0	ND	0.01	Crokett et al., 1974
Five urban soils in the United States	1971	0	ND	<0.03	Carey, 1979

TABLE 3-4 (cont.)

Origin of Soil	Year Sampled	Percent with Positive Level	Concentration* (ppm)	Detection Limit (ppm)	Reference
Five counties in Alabama	NR	2.8	1 out of 36 soils: <0.1	NR	Albright et al., 1974
Ditch from farm area in Nova Scotia	1972-1973	0	ND	NR	Burns et al., 1975
Orchard soils from southern Ontario:					
Apple	1972-1975	5	<0.001 (range: ND-0.004)	<0.0004	Frank et al., 1976
Cherry	1972-1975	0	ND	<0.0004	Frank et al., 1976
Peach	1972-1975	0	ND	<0.0004	Frank et al., 1976

*Values in parentheses indicate the range in concentration.

ND = Not detected

NR = Not reported

TABLE 3-5

Methoxychlor Residue Levels in Aquatic Bottom Sediments

Origin of Sample	Year Sampled	Percent with Positive Level	Concentration* (ppm)	Detection Limit (ppm)	Reference
Lake Michigan:					
Open-water sediment	1970-1971	100	0.0012 (0.00013-0.0066)	10^{-5}	Schacht, 1974
Tributary sediment	1970-1971	100	0.0021 (0.00019-0.175)	10^{-5}	Schacht, 1974
North Saskatchewan River following injection of methoxychlor	1972	50%	0.07 (0.05-0.10)	<0.01	Fredeen et al., 1975
Lake Superior	NR	0	ND	0.01	Glass et al., 1977
Nova Scotia:					
Habitant Creek	1972-1973	0	ND	NR	Burns et al., 1975
Natural drainage ditch	1972-1973	0	ND	NR	Burns et al., 1975
Lake Nakuru, Kenya	1975	0	ND	NR	Greichus et al., 1978
Subarctic Salt Marsh, James Bay, Canada	1979	12.5	1 of 8: <0.05	<0.05	Glooschenko and Sampson, 1979
James River near Windmill Point, VA:	1976	NR	<0.006	0.006	Saleh et al., 1978

*Values in parentheses indicate the range in concentration.

NR = Not reported; ND = not detected

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TABLE 3-6

Methoxychlor Residue Levels in Household Dust

Origin	Year Sampled	Number of samples	Percent with Positive Level	Average Concentration;* ppm in positive sample	Detection Limit (ppm)	Reference
Weld County, CO						
Control group	1968	182	43	6.1 (1.5-28.6)	1.5	Starr et al., 1974
Farmer	1968	45	100	14.9 (1.6-102.9)	1.5	Starr et al., 1974
Pesticide formulator	1968	95	59	18.2 (1.9-144.4)	1.5	Starr et al., 1974
Utah						
Household dust	1970	NR	0	ND	NR	Warnick and Eldredge, 1972
Caribbean Island (Bahamas)						
Household dust	1970-1971	NR	100	33.7	NR	Davies, 1975
Exterior soil	1970-1971	NR	73.3	0.6	NR	Davies, 1975

*Values in parentheses indicate the range in concentration.

ND = Not detected

NR = Not reported

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The inhalation of household dust in areas where methoxychlor is used as a pest control agent may be a significant route of human intake of methoxychlor. The human intake of methoxychlor from this route cannot be estimated, even qualitatively; however, intake from this and other sources will be reflected in the blood level of methoxychlor or its metabolites (discussed in Section 3.7.).

3.5. FOODS

Methoxychlor has been detected in a number of foods eaten by humans including fish (Fredeen et al., 1975; Schacht, 1974; Glass et al., 1977), edible aquatic organisms (Bedford et al., 1968; Buggs et al., 1967), dairy products (Johnson and Manske, 1977; Duggan et al., 1966), poultry products (Stadelman, 1973), grains and cereals (Duggan et al., 1966), fruits (Duggan et al., 1966), and leafy vegetables (Duggan et al., 1971). The frequency of occurrence of methoxychlor in these foods is low. Duggan et al. (1983) reported that between 1971 and 1976 (inclusive), methoxychlor was found in 24 of 1980 (1.2%) composite samples of food. This represents an intake of between 0.1 and 0.8 µg methoxychlor/day for a 16- to 19-year-old male.

The daily dietary intake of methoxychlor for the years such data are available, the frequency of occurrence, and the average concentrations of methoxychlor in contaminated foods of different categories are shown in Table 3-7. The commodities sampled during the years 1964 through 1973 were foods eaten by adults. It can be concluded from Table 3-7 that the level of methoxychlor in foods in the United States may have decreased, although concentrations in dairy products continue.

TABLE 3-7

Dietary Intake, Frequency of Occurrence, and Concentrations of Methoxychlor in Total Diet Samples[a]

Years Sampled[b]	Daily Intake (mg)	Total Diet Samples										Reference
		Dairy Products		Meat, Fish and Poultry		Grains and Cereals		Leafy Vegetables		Fruits		
		Percent with Residue	Average Conc.[c] (ppm)	Percent with Residue	Average Conc.[c] (ppm)	Percent with Residue	Average Conc.[c] (ppm)	Percent with Residue	Average Conc.[c] (ppm)	Percent with Residue	Average Conc.[c] (ppm)	
1964-1969	<0.001	0.5	0.003	1.4	<0.005	3	<0.001	0.7	<0.001	0	ND	Duggan et al., 1971
1969-1970	0.001	20	0.005	0	ND	0	ND	0	ND	3.3	0.023	Duggan and Corneliussen, 1972; Corneliussen, 1972
1970-1971	NA	10	0.006	0	ND	3.3	<0.005	0	ND	0	ND	Manske and Corneliussen, 1974
1971-1972	NA	2.9	<0.005	0	ND	0	ND	0	ND	2.9	0.015	Manske and Johnson, 1975
1972-1973	NA	16.7	<0.048	0	ND	3.3	NR	0	ND	0	ND	Johnson and Manske, 1976
1973-1974	NA	23	0.052	0	ND	0	ND	0	ND	0	ND	Manske and Johnson, 1977
1974-1975	NA	10	<0.023	0	ND	0	ND	0	ND	0	ND	Johnson and Manske, 1977
1975-1976	NA	15	0.079	0	ND	0	ND	0	ND	0	ND	Johnson et al., 1981

[a]Methoxychlor has never been detected in potatoes, legume vegetables, root vegetables, oils, fats and shortenings, sugar and adjuncts, and beverages.

[b]Commodities sampled during 1964-1973 were foods for adults; those sampled during 1974-1975 were foods for infants and toddlers.

[c]Average of the samples with residue.

Conc. = Concentration

ND = Not detected

NA = Not applicable because the sampling does not represent a nationwide survey

NR = Not reported

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3.6. HUMAN BLOOD AND MILK

The blood levels of pesticides in pregnant women in the Jackson and Mississippi Delta areas were monitored during the period 1973 to 1974 (Lloyd et al., 1974). In the 122 samples analyzed in this study, the methoxychlor concentrations ranged from 0-2.5 ppb, with a mean value of 0.7 ppb. No methoxychlor, however, could be detected in the blood of the general population, farmers and pesticide formulators (626 total) (both male and female) in Colorado during 1968 (5 ppb detection limit) (Starr et al., 1974). Since the method of Lloyd et al. (1974) had an order of magnitude greater sensitivity, Starr et al. (1974) may not have been able to detect methoxychlor levels.

Another source of concern is pesticide contamination of human milk. If pesticides are present in mothers' milk, they may be transferred to the infants. Milk samples from 50 women living in Leiden and the surrounding area in Western Netherlands were examined for the presence of organochlorine pesticides (Tuinstra, 1971). Although a few other pesticides were detected, no methoxychlor could be found in any of these samples (limits of detection were not stated for methoxychlor; however, the detection limits for DDT were 0.01 ppm, for DDE and DDD, 0.005 ppm, and for 1,2,3,4,5,6-hexachlorocyclohexane and heptachlor epoxide, 0.002 ppm).

4. PHARMACOKINETICS

4.1. ABSORPTION

Quantitative information on the absorption of methoxychlor by laboratory animals was not located in the available literature. That methoxychlor is absorbed from the GI tract and skin can be inferred from the systemic effects in animals following exposure to methoxychlor by these routes (Section 5).

4.2. DISTRIBUTION

Methoxychlor does not accumulate to any appreciable extent in the tissues of animals. No methoxychlor was detected in the liver or adipose tissue of adult rats or in the carcass, brain or liver of weanling rats of any of four generations maintained on diets containing methoxychlor in concentrations of 0.078-0.116 ppm (mg/kg diet) (Adams et al., 1974). The diets contained other insecticides (DDT, DDE, DDD, dieldrin, lindane, BHC, heptachlor epoxide and Perthane) in ratios that simulated those found in the food supply of the United States, although the concentrations were 200 times higher. Villeneuve et al. (1972) detected no methoxychlor in fat, liver, heart or brain tissue of three male Wistar rats maintained on diets containing 20 mg methoxychlor/kg diet for 350 days. Low levels of the insecticide were detected in the perirenal fat of male and female rats fed methoxychlor at concentrations of 25, 100 and 500 mg/kg diet for up to 18 weeks (Kunze et al., 1950). The levels in fat were detectable (limit of detection was 1 µg/g) after 4 weeks at the high dietary concentration and after 9 weeks at 100 mg/kg diet. The levels in the fat of rats fed at the 500 mg/kg diet level were higher than in 100 mg/kg diet rats. At 2 weeks after the exposure was terminated, no residues were detected. In rats fed methoxychlor at the 25 mg/kg diet level, no methoxychlor was detected in the fat tissue at

any sampling period (4, 9, 13 or 18 weeks). The ratio of the concentration of methoxcyhlor in the perirenal fat to the concentration in the diet, defined as the storage ratio for fat, was ~0.05 at 9 and 4 weeks (for 100 and 500 mg/kg diet levels, respectively) and declined to 0.01-0.03 at 18 weeks, indicating the small degree of accumulation in fat. Similar fat storage ratios (0.01-0.06) were found in female rats fed methoxychlor at levels as high as 1000, 2500 and 5000 mg/kg diet for 6 or 18 weeks (Harris et al., 1974). Rats that received methoxychlor in the diet for 2 years at concentrations of 25, 200 or 1600 mg/kg diet had fat storage ratios of ~0.15, 0.02 and 0.01, respectively (Hodge et al., 1952). Methoxychlor was detected in the kidneys of the rats at the 200 and 1600 mg/kg diet levels with storage ratios of 0.01 and 0.02. Very low levels of methoxychlor residues were detected in the kidneys of rats in the low-dose group and in the liver and brain of rats of all treated groups, but quantitation was imprecise. Low levels of methoxychlor were detected in the fat, kidney, liver and brain of dogs fed 20-300 mg methoxychlor/kg bw/day for 1 year.

4.3. METABOLISM

Early information regarding the metabolism of methoxychlor was obtained from analysis of the urine of animals treated with the insecticide. Organic chlorine was found in the urine of rabbits that received 4-15 oral doses of 200 mg methoxychlor/kg bw/day by gavage in olive oil (Smith et al., 1946). No unchanged methoxychlor was detected in the urine of rats fed the insecticide in the diet (Woodard et al., 1948). Adult male rats injected intravenously with ^{14}C-ring-labeled methoxychlor excreted radiolabeled metabolites of greater water solubility than the parent compound in the urine, feces and bile (Weikel, 1957). The metabolites were characterized by ion exchange column chromatography as strongly acidic anions. Evidence that detoxication

of methoxychlor results mainly from metabolism in the liver was presented by Laug and Kunze (1951) and Weikel and Laug (1958). Concurrent or pretreatment of rats with carbon tetrachloride at doses that caused liver damage resulted in enhanced toxicity of a single intravenous dose of methoxychlor. Approximately 10-100 times higher levels of methoxychlor in abdominal fat and livers of the rats resulted from treatment with this combination of chemicals than when methoxychlor was administered alone (Laug and Kunze, 1951). The biliary excretion of metabolites of methoxychlor was inhibited in a dose-related manner when the carbon tetrachloride pretreatment dose was varied (Weikel and Laug, 1958).

Kapoor et al. (1970) treated female Swiss mice with single oral doses (50 mg/kg bw) of ^{3}H-ring-labeled or ^{14}C-ring-labeled methoxychlor in olive oil:acetone (4:1) and analyzed the feces and urine. The major metabolites, identified by TLC, were the monophenol [2-(p-methoxyphenyl)-2-(p-hydroxyphenol-1,1,1-trichloroethane] and the bisphenol [2,2-bis-(p-hydroxyphenyl)-2-1,1,1-trichloroethane]. These products would result from the O-demethylation of methoxychlor. The dehydrochlorination product of the bis-phenol [2,2-bis(p-hydroxyphenyl)-1,1-dichloroethylene] was also identified. Other identified products included bis(p-hydroxyphenyl) acetic acid and p,p'-dihydroxybenzophenone. The pathway for these conversions is illustrated in Figure 4-1.

In female mice treated as described above, the 48-hour urine and feces contained 7, 30 and 23% of the excreted radioactivity as unchanged methoxychlor, the monophenol and the bisphenol, respectively (Coats et al., 1979).

O-demethylation of methoxychlor by microsomal enzymes was indicated by in vitro experiments. A Type I spectral shift (i.e., a peak at 385 nm and a trough at 420 nm) in the optical difference spectrum of cytochrome P-450 was

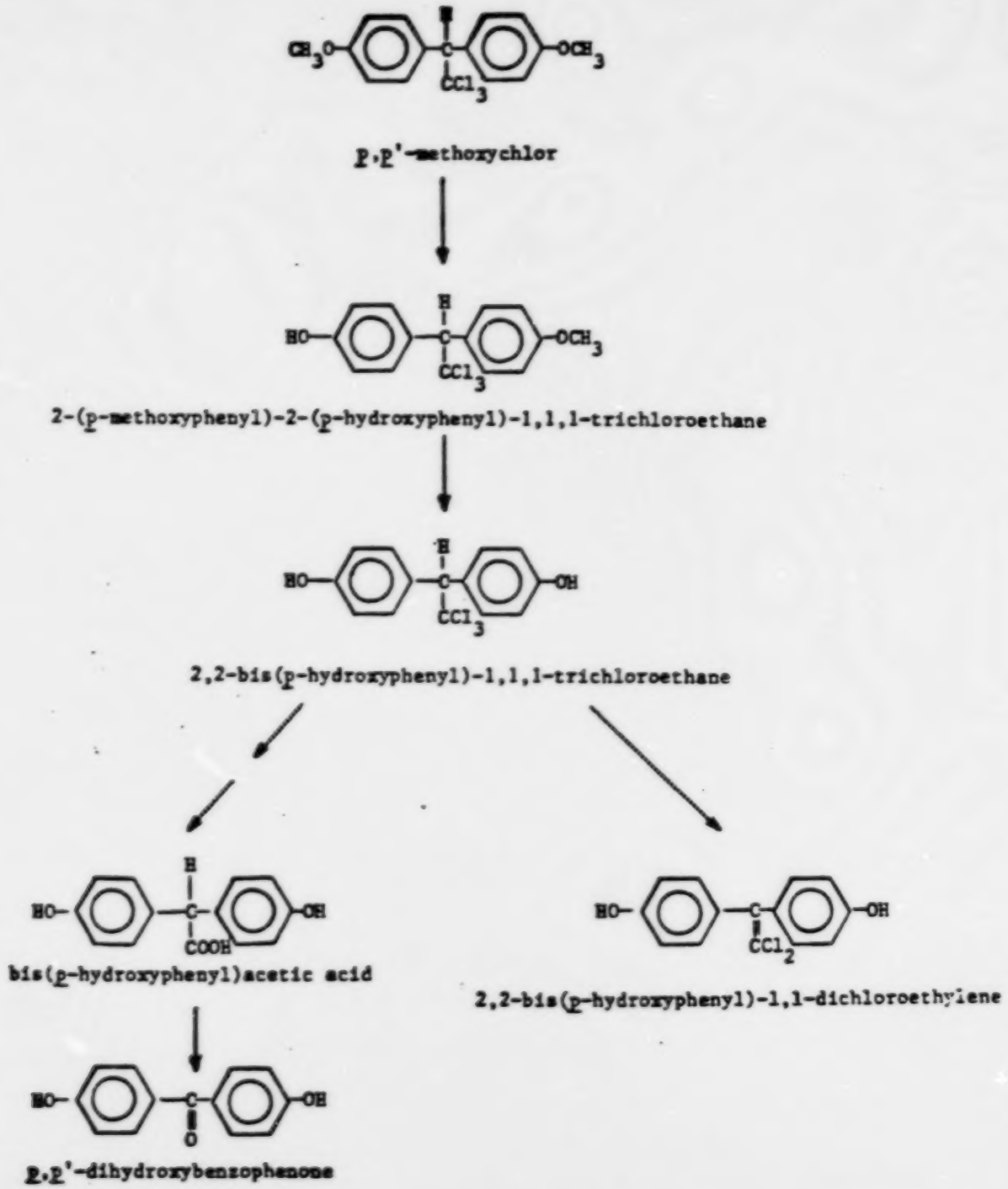

FIGURE 4-1

Postulated Metabolic Pathway for Methoxychlor in Rodents

Source: Kapoor et al., 1970

observed when methoxychlor was incubated with hepatic microsomes from rats, mice and rabbits. The shift indicated that methoxychlor was bound to the cytochrome P-450 (Kulkarni et al., 1975; Donovan et al., 1978). When radiolabeled methoxychlor was incubated with rat or mouse liver microsomes in the presence of NADPH, the monophenol and bisphenol, as well as formaldehyde, were identified as in vitro metabolites (Kapoor et al., 1970; Bulger et al., 1978a; Coats et al., 1979; Ousterhout et al., 1979, 1981). Addition of hexobarbital or SKF-525A, modifiers of microsomal enzyme activity, to the incubation system resulted in inhibition of formaldehyde evolution, further supporting the involvement of the microsomal enzymes in O-demethylation of methoxychlor (Bulger et al., 1978a).

4.4. EXCRETION

The 24-hour urine and feces of Swiss female mice treated with a single oral dose of ^{3}H-ring-labeled methoxychlor at 50 mg/kg bw contained 98.3% of the administered radioactivity, the majority of which was found in the feces (Kapoor et al., 1970). The feces contained 90% and the urine contained 10% of excreted radioactivity. No radioactivity was detected in the excreta after 11 days postexposure.

Following the intravenous injection into adult male rats of ^{14}C-ring-labeled methoxychlor at a dose of 3 mg/kg bw in a saline-lecithin-oil emulsion, ^{14}C-methoxychlor disappeared rapidly from the blood and accumulated rapidly in the liver (Weikel, 1957). Fecal excretion of radioactivity amounted to ~50% of the administered dose in 4 days, indicating substantial excretion in the bile. Urinary elimination of radioactivity was 5-10% over 4 days, although the 24-hour urine contained the majority of the total urinary radioactivity. Biliary excretion of radioactivity was confirmed in rats with cannulated bile ducts and amounted to ~20% in the first hour and

~50% over the next 6 hours after dosing. Enterohepatic recycling by intact rats was indicated by the finding that the bile duct cannulated rats excreted only 0.1-0.2% of administered radioactivity in 6 hours, compared with the higher percentage of radioactivity in the urine of intact rats.

5. EFFECTS

5.1. CARCINOGENICITY

There are a number of carcinogenicity studies of methoxychlor in mice and rats (Nelson and Fitzhugh, 1951; Hodge et al., 1952, 1966; Radomski et al., 1965; Davis, 1969; Deichmann et al., 1967; NCI, 1978) and dogs (Nelson and Radomski, 1953), for which negative results were reported. A re-evaluation of histological slides from these studies by Reuber (1978, 1979a,b, 1980) indicated that methoxychlor had a positive carcinogenic effect in the rats and mice; however NCI (1978), IARC (1979) and CAG (U.S. EPA, 1983) have concluded that the contentions of the original investigators (i.e., that methoxychlor was not carcinogenic in their studies) are best supported by the pathological data. In two reviews of the NCI bioassay program (Griesemer and Cueto, 1980; Harper et al., 1982), it was recommended that the negative results of NCI bioassays be considered as inconclusive rather than negative. Therefore, in the following discussion, the results of the original investigators' analyses are reported whenever possible.

The possibility that exposure of rats to several agents (thiourea or aldrin, Aramite, DDT and methoxychlor) simultaneously may result in synergism of carcinogenic effects was investigated in a series of experiments (Radomski et al., 1965; Deichmann et al., 1967). The rats were of the Osborne-Mendel strain and the chemicals were administered in the diet for 2 years. Only the results of the portions of the experiment in which methoxychlor was administered alone are reported in this discussion. Groups of 30 male and 30 female rats were maintained on a diet containing 0 or 80 mg methoxychlor/kg diet (Radomski et al., 1965). At the end of 2 years, the rats were killed and examined for tumors, especially of the liver. No treatment-related increase in total tumors was observed. One female control

had a liver tumor. In a similar experiment, a group of 30 male and 30 female rats received 1000 mg methoxychlor/kg diet for 2 years, and no treatment-related increase in tumor incidence was observed compared with controls (Deichmann et al., 1967). None of the rats had liver tumors.

Groups of 12 male and 12 female Osborne-Mendel rats maintained on diets containing technical grade methoxychlor at concentrations of 0, 25, 100, 500 or 2000 mg/kg diet for 2 years did not develop malignant tumors in the liver (Nelson and Fitzhugh, 1951). The rats had been examined for gross lesions; histological examination was performed on the gross lesions. The following lesions were observed: hyperplastic foci in the liver of one rat at the 100 mg/kg diet level, a liver nodule in a 500 mg/kg diet group rat and benign hepatic cell adenomas in four rats in the 2000 mg/kg diet group.

Groups of 25 male and 25 female rats of unspecified strain received technical grade methoxychlor at levels of 0, 25, 200 or 1600 mg/kg diet for 2 years (Hodge et al., 1952). Early mortality caused by infections (4-30%) during the first year reduced the number of rats at risk. At the end of 2 years, the survivors were killed. No treatment-related increased incidences of tumors were found in heart, lungs, spleen, stomach, small intestine, large intestine, adrenal, kidney, testes, bladder, bone marrow, brain or any other organs with gross lesions. The liver was not routinely examined.

In an NCI (1978) bioassay, groups of 50 male and 50 female Osborne-Mendel rats were maintained on diets containing technical grade methoxychlor (95%) for 78 weeks and were observed for an additional 33 weeks. The TWA concentrations were 448 and 845 mg/kg diet for low and high dose males, respectively, and 750 and 1385 mg/kg diet for low and high females, respectively. Controls consisted of groups of 20 male and 20 female rats of the same strain with no methoxychlor in the diet. Necropsy and comprehensive

histological examinations were performed on all rats that died spontaneously, were sacrificed when moribund or were sacrificed at the end of the study. Cannibalism and autolysis precluded examination of some tissues. No treatment-related increase in tumor incidence was observed for any group compared with controls. Hemangiosarcomas were observed at a higher incidence in treated male than control male groups, but the incidence was not dose-related and the difference was not statistically significant.

NCI (1978) also studied the carcinogenic potential of methoxychlor in groups of 50 male and 50 female B6C3F1 mice. Control groups contained 20 male and 20 female mice. The methoxychlor was administered in the diet for 78 weeks at TWA concentrations of 1746 and 3491 mg/kg diet for the low and high dose males, respectively, and 997 and 1994 mg/kg diet for the low and high dose females, respectively. The mice were observed for 15 weeks after dietary exposure to methoxychlor was discontinued. Necropsy and comprehensive histological examination was performed on all mice that died spontaneously, were killed when moribund or were sacrificed at the end of the study. No treatment-related or statistically significant increase in tumor incidence was observed for any treated group compared with controls.

Reuber (1980) reviewed an unpublished study in mice (Davis, 1969) that was performed for the FDA. Groups of 100 male and 100 female mice of two different strains (BALB/c and C3H) were maintained on diets containing 0 or 750 mg methoxychlor/kg diet for 2 years. A preliminary survey of the results of the histopathologic examination indicated to Davis (1969) that methoxychlor was not carcinogenic; however, the results obtained by Davis (1969) were not available for this discussion. Reuber (1980) re-evaluated the slides and the results he obtained are presented in Table 5-1.

TABLE 5-1

Tumor Incidence in Mice Ingesting Methoxychlor in the Diet[a,b]

Dose (ppm)	Strain	Sex	Site of Tumor	Incidence	Percent of Animals with Tumors
0	BALB/C	M	testis	8/71	11
750	BALB/C	M	testis	27/51	53
0	BALB/C	M	liver	3/73	4
750	BALB/C	M	liver	18/67	27
0	BALB/C	F	liver	2/89	2
750	BALB/C	F	liver	12/96	13
0	C3H	M	liver	23/96	24
750	C3H	M	liver	43/92	47
0	C3H	F	liver	11/99	11
750	C3H	F	liver	15/83	18

[a]Source: Reuber, 1980

[b]A reevaluation of the FDA study

In another FDA study (Nelson and Radomski, 1953) reviewed by Reuber (1980), methoxychlor was fed to one male and three female dogs at a dose of 300 mg/kg bw/day for up to 3.5 years. One female dog died at 260 days and the male dog died at 105 days. Reuber (1980) evaluated the histological slides from the remaining animals and found that one female had a liver carcinoma and the other fibrosis of the liver. The interpretation of these findings is difficult because of the small number of animals and the lack of controls.

Hodge et al. (1966) tested methoxychlor as a complete carcinogen on the shaved skin of 50 male and 50 female C3H/Anf mice. The insecticide was applied in acetone once per week for the lifespan of the mouse in amounts of 0.1 or 10.0 mg/mouse/week. On gross and histological examination of the skin of 28 low dose and 23 high dose mice, no lesions were observed. Gross examination of internal organs revealed no treatment-related lesions when compared with control mice. Subcutaneous injection of a single dose of methoxychlor (10 mg/mouse) to 50 male and 50 female mice also resulted in no gross or histopathologic changes compared with controls (Hodge et al., 1966).

5.2. MUTAGENICITY

Technical grade methoxychlor has been tested for mutagenicity in a variety of assays in prokaryotic and eukaryotic systems with mainly negative results, regardless of the presence of metabolic activation systems. A summary of these studies is presented in Table 5-2. Methoxychlor was negative for reverse mutation with and without metabolic activation by the S-9 fraction prepared from the livers of Aroclor pretreated rats in every strain of Salmonella typhimurium and Escherichia coli tested (Ames assay) (Probst et al., 1981; Simmon, 1979; Waters et al., 1982; Grant et al., 1976; Wildeman

TABLE 5-2

Mutagenicity Testing of Methoxychlor

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium G46, TA1535, TA1000, C3076, TA1537, D3052, TA1538, TA98	plate incorporation	10,000-fold concentration range	± S9	- -	The response was negative in all strains tested with and without metabolic activation.	Probst et al., 1981
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA100, TA98	plate incorporation	6 concentrations up to 10 mg/plate	± S9	- -	The response was negative in all strains tested with and without metabolic activation.	Simmon, 1979; Waters et al., 1982
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA98	plate incorporation	2-200 µg/plate	± S9	- -	Both technical grade methoxychlor and a purified preparation were tested, both with negative results in all strains. See text for further discussion.	Grant et al., 1976
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	0.2-100 µg/plate	± S9	- -	The response was also negative in both strains when the S-14 fraction from wheat or corn homogenates was used as the activating system.	Wildeman and Nazar, 1982
Reverse mutation	Escherichia coli WP2, UVRA-	plate incorporation	10,000-fold concentration range	± S9	- -	The response was negative in both strains with and without activation.	Probst et al., 1981
Reverse mutation	E. coli WP2	plate incorporation	6 concentrations up to 10 mg/plate	± S9	- -	NC	Simmon, 1979; Waters et al., 1982
Reverse mutation	E. coli WP2	spot test	1 mg/disc	- S9	-	NC	Ashwood-Smith et al., 1972

TABLE 5-2 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
DNA repair	E. coli pol A⁻ (P3478) pol A⁺ (W3110)	spot test	NR	- S9	no test	No test - ambiguous results (i.e., no growth inhibition on either test plate)	Simmon, 1979; Waters et al., 1982
Rec assay	Bacillus subtilis rec A⁻ (M45)) rec A⁺ (H17)	spot test	NR	- S9	no test	No growth inhibition on either test plate	Simmon, 1979; Waters et al., 1982
DNA damage induced mitotic recombination	Saccharomyces cerevisiae D3	NR	5 concentrations	± S9	- -	NC	Simmon, 1979; Waters et al., 1982
Sex-linked recessive lethal	Drosophila melanogaster	exposure of male flies	NR	NA	-	<0.2% increase in mutation over background	Waters et al., 1982
Sex-linked recessive lethal	D. melanogaster	male flies injected in the abdomen	up to 0.2 µl/fly	NA	-	0.2 µl/fly of 0.1% solution was the highest dose tolerated.	Benes and Sram, 1969
forward mutation	mouse lymphocytes L5178Y/TK⁺⁻	cell culture	NR	± S9	±	NC	Myhr et al., 1981
Cell transformation	mouse BALB/3T3	cell culture	0.1-10 µg/ml	NR	+	Dose-related increase in number of foci/plate above control at concentrations up to 2.0 µg/ml (3-fold increase at 2.0 µg/ml)	Dunkel et al., 1981
Cell transformation	Rauscher murine leukemia virus-infected rat embryo cells	cell culture	0.12-12 µg/ml	NR	-	Negative in cultures taken through 11 passages	Dunkel et al., 1981

TABLE 5-2 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Cell transformation	Rauscher murine leukemia virus infected rat embryo cells	cell culture	12 µg/5.2 x 10^4 cells	NR	-	NC	Traul et al., 1981
Cell transformation	Syrian hamster embryo cells	cell culture	0.05-50 µg/mL	NR	-	NC	Pienta, 1980; Dunkel et al., 1981
Unscheduled DNA synthesis	primary rat hepatocytes	cell culture	8 concentrations 0.5-1000 nmol/mL	NR	-	100 nmol/mL was the highest nontoxic concentration	Probst et al., 1981
Unscheduled DNA synthesis	human lung fibroblasts W138	cell culture	5 concentrations	± S9	- -	No significant increase in ^{3}H-thymidine incorporation	Simmon, 1979; Waters et al., 1982

NC = No comment

NR = Not reported

NA = Not available

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and Nazar, 1982; Ashwood-Smith et al., 1972). Methoxychlor was also negative in this assay when homogenates prepared from corn or wheat were used as the activating system (Wildeman and Nazar, 1982). The plant enzymes were used in order to determine if different metabolites of methoxychlor, presumably arising from biotransformation by plants, were mutagenic. Purified methoxychlor was also negative (Grant et al., 1976). Grant et al. (1976) tested the possibility that some of the impurities of technical grade methoxychlor, which has been reported to be ~93% pure (Lamoureux and Fell, 1980), were mutagenic in the Ames assay. The compounds tested were tetrakis (p-methoxyphenoxy)-ethylene; 3,6-dimethoxy-9,10-bis (p-methoxyphenyl)phenanthrene and 3,6,11,24-tetramethoxydibenzo(g,p)chrysene. The assay system was the same as that used for technical grade methoxychlor (see Table 5-2). The chrysene derivative showed a weak positive response in strain TA1538 and a definite positive response in strain TA98 with, but not without, metabolic activation. It is possible that the other impurities may have been positive if tested at higher concentrations. Other contaminants of methoxychlor may be mutagenic; however, the activity may be masked by the toxicity of technical grade methoxychlor to bacteria.

Ambiguous results were obtained when technical grade methoxychlor was tested for DNA-damage in repair deficient and proficient strains of E. coli and Bacillus subtilis (Simmon, 1979; Waters et al., 1982).

Technical grade methoxychlor was negative in most assays using eukaryotic indicators. These include DNA damage induced mitotic recombination in Saccharomyces cerevisiae (Simmon 1979; Waters et al., 1982), sex-linked recessive lethal mutations in Drosophila melanogaster (Waters et al., 1982; Benes and Sram, 1969), cell transformation in Rauscher murine leukemia virus-infected rat embryo cells (Dunkel et al., 1981; Traul et al., 1981)

and in Syrian hamster embryo cells (Pienta, 1980; Dunkel et al., 1981) and unscheduled DNA synthesis in primary rat hepatocytes (Probst et al., 1981) and human lung fibroblasts (Simmon, 1979; Waters et al., 1982).

Positive responses were found for forward mutation in mouse lymphocyte cultures with, but not without, metabolic activation (Myhr et al., 1981) and for cell transformation in mouse BALB/3T3 cultures (Dunkel et al., 1981).

5.3. TERATOGENICITY

Only one study testing the possible teratogenicity of methoxychlor was available. Khera et al. (1978) treated pregnant Wistar rats (20 per group) with technical grade methoxychlor in corn oil by gavage at doses of 0, 50, 100, 200 or 400 mg/kg bw/day on days 6-15 of gestation. Day 1 of gestation was defined as the morning on which a sperm-positive vaginal smear was observed. Groups of pregnant rats were similarly treated at doses of 0, 100, 200 or 400 mg/kg bw/day of a methoxychlor formulation that consisted of 50% of the technical grade product and 50% unknown ingredients. The dams were sacrificied on day 22 of gestation. There was a significant reduction in maternal body weight gain ($p<0.05$) in dams treated with technical grade methoxychlor at all doses at day 15 and at 200 and 400 mg/kg at day 22. Following necropsy and removal of uteri, only the 400 mg/kg level dams had significantly reduced body weight compared with controls, indicating that the reduced body weight in the high dose group was due to an effect on the dam, rather than small litter sizes or reduced fetal body weight. For the methoxychlor formulation, similar findings of reduced body weight in dams during gestation were observed; however, after uteri were removed, the body weight of dams was significantly lower than controls only for the 100 and 200 mg/kg groups and not for the 400 mg/kg group. Reduction in body weight

was the only observed sign of maternal toxicity. The teratogenic and fetotoxic effects are presented in Table 5-3. At the high-dose levels (200 and 400 mg/kg), there were reduced numbers of live fetuses and increased percentage resorptions. Fetal weights were significantly reduced ($p<0.05$) in the groups receiving 200 and 400 mg technical grade methoxychlor/kg bw. There were significantly greater percentages of malformed fetuses at the 200 and 400 mg/kg dose levels compared with controls for both treatments. The type and incidence of anomalies are presented in Table 5-3.

5.4. OTHER REPRODUCTIVE EFFECTS

Harris et al. (1974) exposed groups (17-25 animals/group) of female Sprague-Dawley rats to diets of methoxychlor for 6 weeks before mating and throughout gestation and lactation. The offspring were continued on the diets after weaning. At a dietary level of 1000 mg/kg diet, there was no effect on reproduction in dams. In 41% of the female offspring there was early vaginal opening. Reduced numbers of offspring mated, and decreased reproductive performance was observed in males. Virgin adults had 33% decreased ovarian weight. At a dietary level of 2500 mg/kg diet, only 9/20 of the adult females mated and only one of the mated dams littered. These effects were reversible when treatment ceased. Early vaginal opening occurred in female offspring. The ovarian weight of virgin adults was decreased to 66% of control. At a dietary level of 5000 mg/kg diet, only 2/25 of the adult females mated. After 5 weeks of treatment, the female adults had constant estrus, 20% increased uterine weight and 66% decreased ovary weight.

The reproductive performance of rats exposed to methoxychlor <u>in utero</u> was studied by Gellert and Wilson (1979). Pregnant Sprague-Dawley rats received methoxychlor (in 5% ethanol in sesame oil) by gavage at doses of 30

TABLE 5-3

The Prenatal Effects of Methoxychlor, Technical Grade and Formulation, Given to Rats by Intubation on Days 6 through 15 of Gestation[a]

	Methoxychlor, Technical Grade Dose (mg/kg)					Methoxychlor Formulation Dose (mg/kg)			
	0	50	100	200	400	0	100	200	400
Number of rats with live fetuses[b]	19	18	20	16	9	17	18	17	15
Number of corpora lutea per pregnancy[b]	13.3±0.4	12.8±0.6	13.3±0.3	13.7±0.7	11.4±1.1	14.0±0.5	13.9±0.4	13.8±0.5	13.5±0.5
Number of live fetuses per pregnancy	12.2±0.5	11.0±0.8	11.6±0.5	7.4±1.2[c]	2.7±1.4[c]	111.7±0.8	12.1±0.6	9.8±0.8	5.0±0.9[c]
Dead fetuses and resorbed fetuses x 100/total implant sites	3	11	11	40[c]	70[c]	8	7	19[c]	60[c]
Fetal weight (g)[b]	5.2±0.1	5.2±0.1	4.9±0.1	4.1±0.4[c]	3.3±0.8[c]	5.0±0.1	5.0±0.1	4.9±0.1	4.2±0.5
Number of anomalous fetuses[d]/number examined	11/230	25/209	35/232	26/117[c]	16/24[c]	14/199	20/218	40/167[c]	25/75[c]
Number of anomalous litters/total examined	5/19	11/19	13/20	11/14	6/6	9/18	8/18	14/17	11/13
Anomalies (number of fetuses affected)									

TABLE 5-3 (cont.)

	Methoxychlor, Technical Grade Dose (mg/kg)					Methoxychlor formulation Dose (mg/kg)			
	0	50	100	200	400	0	100	200	400
Wavy ribs, uni- and bilateral	6/154	18/138	31/155[c]	22/80[c]	16/17[c]	3/138[c]	12/149[c]	30/117[c]	22/52[c]
Extra ribs, uni- and bilaterial	3	6	3	2	NR	5	5	3	NR
Sternebrae nonapposed	NR	NR	NR	NR	NR	NR	NR	1	2
Sternebrae missing or unossified	NR	1	NR	NR	NR	NR	NR	NR	2
Calvarium, delayed ossification	2	5	NR	NR	NR	NR	NR	10	14
Bent scapula, radius or ulna	NR	3	1	NR	5	NR	NR	3	2
Runted fetuses	2	NR	1	NR	1	NR	NR	NR	NR
Subcutaneous hematoma	NR	2	NR	NR	NR	NR	NR	NR	NR
Right atrium enlarged	NR	NR	NR	2	1	NR	NR	NR	NR
Encephaly	NR	NR	NR	NR	NR	NR	2	NR	NR

[a]Source: Khera et al., 1978

[b]Mean ± S.E.

[c]$p<0.05$

[d]A fetus may have more than one anomaly.

NR = Not reported

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mg/kg bw/day on days 14-20 of gestation. Female offspring had significantly increased body weight compared with controls ($p<0.001$). There was no effect on the weight of ovaries, uteri or adrenals of female offspring at 6 months of age or on fertility of male offspring.

A uterotropic effect of methoxychlor in mice and rats was observed following acute oral exposure to the insecticide (Tullner, 1961). Ovariectomized NIH mice given totals of 0.5, 1.0 or 5.0 mg methoxychlor in sesame oil over 3 days had 117, 273 and 563% increased uterine weights compared with controls. Sprague-Dawley rats that had been ovariectomized and adrenalectomized received a total of 20 mg methoxychlor over 3 days and had 192% increased weight of uterus over controls. Hypophysectomized rats similarly treated had uterine weights >241% of controls.

Studies regarding the effects of methoxychlor on the reproductive organs of experimental animals following subchronic oral exposure have also been reported and are presented in detail in Section 5.5. A brief discussion of the reproductive effects is presented here. Shain et al. (1977) found that dietary administration of methoxychlor to rats at 2000 mg/kg diet for 90 days resulted in 23% decreased body weight, 11% decreased testicular weight and 40% decreased ventral prostate weight. Similar testicular effects were found in rats maintained on diets containing 10,000 mg methoxychlor/kg diet for <55 days (Tullner and Edgcomb, 1962; Hodge et al., 1950). Hodge et al. (1950) also described histopathologic changes in the testes of rats, including reduced numbers of spermatocytes in seminiferous tubules, azoospermia in the tubular lumen, atypical spermatozoa in the tubules, severe atrophy of seminiferous tubules and necrotic primary spermatocytes.

Changes in the reproductive organs of miniature swine were observed by Bierbower (1966, 1967a,b) and Tegeris et al. (1966). Female swine receiving

1-2 g/kg bw/day of methoxychlor in the diet for up to 5.5 months had prolapsed vaginae, swollen vulvae, mammary gland hyperplasia, endometrial hyperplasia, uterine cysts and premature heat in offspring (Bierbower, 1966, 1967a,b). Male swine had testicular atrophy and castrated males had mammary hypertrophy. Similar effects were observed in miniature swine treated with up to 4.0 g/kg bw/day of dietary methoxychlor (Tegeris et al., 1968). Studies regarding the mechanism by which methoxychlor exerts its reproductive effects have been reviewed in detail by U.S. EPA (1983) and will not be detailed here. Briefly, technical grade methoxychlor may compete with estrogen for cytoplasmic receptor binding sites (Kupfer and Bulger, 1976). Evidence from in vivo and in vitro studies that compared the estrogenic action of technical and purified methoxychlor and metabolites of methoxychlor indicated that the effect may be due primarily to impurities of the technical grade insecticide (Bitman and Cecil, 1970; Nelson, 1974; Bulger et al., 1978b,c; Bulger et al., 1980) and/or to an in vivo metabolite, perhaps the bisphenol (Bulger et al., 1978b; Kupfer and Bulger, 1979) or the monophenol (Ousterhout et al., 1979, 1981), or both (see Section 3.3.). The antiandrogenic effects of methoxychlor may be explained by evidence that the binding of estrogen to rat testicular cytosolic receptors (Bulger et al., 1978d) and the binding of androgen to rat prostate cytosolic and nuclear androgen receptors (Shain et al., 1977) was inhibited by methoxychlor and/or metabolites. In addition, the in vitro metabolism of testosterone by rat liver microsomes was inhibited by methoxy- chlor (Donovan et al., 1978).

Information regarding reproductive effects of methoxychlor in humans is limited. Wills (1969) reported that ingestion for 4-6 weeks of 0.5, 1.0 or 2.0 mg/kg bw/day of methoxychlor by female volunteers did not affect the

menstrual cycle. Light and electron microscopic examination of testicular biopsies from male volunteers revealed no abnormalities other than a shortening of the neck of spermatozoa. Male volunteers who had ingested 0.5, 1.0 or 2.0 mg/kg bw/day methoxychlor for 6-8 weeks did not have reduced volume of ejaculate (Stein, 1970).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Studies of subchronic oral toxicity of methoxychlor to rats, dogs, swine, monkeys and humans are summarized in Table 5-4. As seen from the table, the most commonly observed effect of subchronic oral exposure to methoxychlor is reduced growth rate. This effect has been observed in rats (Tullner and Edgcomb, 1962; Hodge et al., 1950; Shain et al., 1977; Stein, 1970; Davison and Cox, 1976; Weiss et al., 1970; Haag et al., 1950), dogs and swine (Tegeris et al., 1966). This effect was shown to be due to some factors in addition to refusal of food at a high dietary level (10,000 mg/kg diet) by comparing body weight gain of rats treated with methoxychlor in the diet with pair-fed controls (Hodge et al., 1950; Tullner and Edgcomb, 1962). Davison and Cox (1976) compared body weight gain and food consumption in rats treated with methoxychlor in the diet at 0, 10, 100, 1000 and 10,000 mg/kg diet. One set of animals received food ad libitum. In another set, the 10,000 mg/kg diet group was fed ad libitum, while the 0-1000 mg/kg diet groups were pair-fed. As the concentration of methoxychlor increased, the rats ate correspondingly less food and gained correspondingly less body weight, when allowed the food ad libitum ($p<0.01$). In the pair-fed experiment, only those rats receiving 10,000 mg methoxychlor/kg diet and fed ad libitum had reduced body weight compared with corresponding controls.

TABLE 5-4

Subchronic Oral Toxicity of Methoxychlor[a]

Species/Strain	Sex	No.	Weight/Age	Vehicle	Purity	Dose/Duration	Signs/Symptoms	Reference
Rats/ Sprague-Dawley	M	5-6/ group	NR	diet	technical grade	10,000 mg/kg diet x 33-55 days in pair-fed and nonpair-fed groups	Body weight loss, marked testicular atrophy, decreased weight of seminal vesicles, testes and ventral prostate glands, increase in adrenal weight, cystic tubular nephropathy in kidneys, histopathologic changes in testes and kidneys but not in liver, pancreas or adrenal glands.	Tullner and Edgcomb, 1962
Rats/NR	M&F	20/ group	average weight--54 g/ NR	diet	technical grade	100 mg/kg diet x 45 days	No effect on growth, survival, organ weight, hematology, or histopathologic examination of tissues.	Hodge et al., 1950
						1000 mg/kg diet x 45 days	Small but detectable growth depression, no effect on survival, organ weights, hematology, or histopathologic examination of tissues.	
						10,000 mg/kg diet x 30 days[b]	Marked decrease in testes weight (0.2 g vs. 1.8 g in controls) and development, histologic testicular atrophy, minor decreases in growth rate, red-blood cell counts, and hemoglobin, no histopathologic changes in any organ except testes.	
						30,000 mg/kg diet x 45 days	Marked growth retardation, 8/10 deaths in each of the male and female groups, histologic changes in testes, (but not in liver, kidneys, spleen, heart, stomach, lungs or brain), dramatic decreases in organ weights; no effect on hematology.	

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Species/Strain	Sex	No.	Weight/Age	Vehicle	Purity	Dose/Duration	Signs/Symptoms	Reference
Rats/ Sprague-Dawley	M	12	322 g/ 76-91 days	diet (mixed with aqueous starch)	technical grade	2000 mg/kg diet x 90 days	Marked growth depression, significantly decreased testicular and ventral prostate weights, (11% decrease in testes weight, 23% decrease in body weight, and 40% decrease in ventral prostate weight)	Shain et al., 1977
Rats/ Sprague-Dawley	M&F	NR	NR	intubation: 1% gum tragacanth	NR	0.4, 1.0 or 2.5 g/kg bw/day x 3 months	Dose-related growth retardation in males and females after 4-6 weeks; salivation; alopecia at mid and high doses; no effect on blood chemistry, no histopathological tissue damage, no renal abnormalities; decrease in hepatic triglycerides.	Stein, 1970
Rats/ Sprague-Dawley	NR	12/ group	NR/23 days	diet pair-fed and non-pair-fed (acetone used for mixing in diet)	sigma grade II	10 mg/kg diet x 16 weeks	Slight reduction (not statistically significant) in hepatic storage of vitamin A (7-13%).	Davison and Cox, 1976
						100 mg/kg diet x 16 weeks	Decreased hepatic storage of vitamin A.	
						1000 ppm x 16 weeks	Decreased body weight gain in nonpair-fed rats only.	
						10,000 mg/kg diet x 16 weeks	4/12 deaths; increase in liver weight relative to body weight	
Rats/NR	M	NR	NR/NR	diet	NR	500 and 2500 mg/kg diet x 4 weeks	Body weight loss, decreased food intake, increased hexobarbital sleeping time, elevated pentylenetetrazol and hexafluorodiethyl ether convulsive thresholds; no effect on survival, cardiovascular parameters, liver weight, histopatholgic examination, or spontaneous motor activities.	Weiss et al., 1970
						500 and 2500 mg/kg diet x 52 weeks		

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TABLE 5-4 (cont.)

Species/Strain	Sex	No.	Weight/Age	Vehicle	Purity	Dose/Duration	Signs/Symptoms	Reference
Rats/NR	M&F	14/group	(55-65 g)/ 30 days	diet (dog chow)	recrystal-lized in Pyrax	300,600,900 or 1200 mg/kg diet x 1 year	No effect on survival or growth; histopathologic examination performed on only 1 animal in the 600 and 2500 ppm groups; apparently no animals were evaluated in the 300 or 900 ppm groups; no changes observed in heart, lungs, GI tract, liver, spleen, kidneys, adrenals, pancreas, thyroid, gonads, skeletal muscle or skin.	Haag et al., 1950
						2500 mg/kg diet x 1 year	Growth retardation; no histopathologic changes observed in the one rat examined from the group.	
						5000 mg/kg diet x 1 year	Growth retardation; no increase in mortality, hemosiderosis in spleen in 1 rat; no other histopathologic changes observed in the 7 animals examined in this group.	
						10,000 mg/kg diet x 1 year	7/7 females and 2/7 males died within 10 weeks; emaciation and lack of growth; no tremors observed; hemosiderosis of spleen in 1 rat; no other histopathologic changes observed in 7 animals examined from this group (including brain).	
Dogs/NR	NR	2/group	NR	diet	technical grade	20, 100 and 300 mg/kg bw/day x 1 year	2 deaths, not treatment-related; no effect on growth, hematology, organ weights, urinalysis; no evidence of tissue damage during histopathologic examination of testes, liver, kidneys, spleen, heart, stomach, lungs, brain, large and small intestine, adrenals, bladder, lymph nodes and bone marrow.	Hodge et al., 1952

TABLE 5-4 (cont.)

Species/Strain	Sex	No.	Weight/Age	Vehicle	Purity	Dose/Duration	Signs/Symptoms	Reference
Dogs/beagle	M&F	6/group	5.4-12.8 kg/ 5-9 months	diet	technical grade	1.0 g/kg bw/day x 6 months	Loss of body weight; no effect on behavior, survival time, hematology or clinical chemistry measurements; no histopathologic tissue damage in thyroid, pancreas, adrenals, lungs, heart, liver, stomach, small intestine, large intestine, kidneys, bladder, prostate, testes, uterus, muscle, spleen, bone or mammary tissue.	Tegeris et al., 1966
		N = 8 in the 2.5 g/kg group				2.0, 2.5 or 4.0 g/kg bw/day up to 6 months	Body weight loss; behavioral symptoms: salivation, tremors, mydriasis, hyperesthesia, tonic seizures, tetanic convulsions (survival time in these dogs averaged 22 days), ataxia; dose-dependent increase in SGOT, SGPT, and alkaline phosphatase; dose-dependent absence of adipose tissue from normal depots and congestion of mucosa of small intestine; no effect on hematology; no histopathologic tissue damage.	
		4		intubation; 1% gum tragacanth		2.5 g/kg bw/day x 5 months	No signs or symptoms of toxicity (probably due to vehicle)	
Swine/ miniature	M&F	24 F 4 M	NR/6.5-23.5 months	diet	NR	1 g/kg bw/day for 6-40 weeks; (increased to 2 g/kg bw in 7 animals at 4-12 weeks)	2/28 deaths between 10 and 17 weeks; signs of continuous heat after 21 days, prolapsed vagina; swollen vulva, moderate to severe breast hyperplasia with secretion; pseudocyesis; endometrial hyperplasia in uteri of all females; histopathological examination revealed chronic interstitial renal fibrosis in all treated pigs, uterine cysts, hypotrophic testes in 2/4 boars, moderate to severe fatty liver changes in 4 females, offspring had swollen vulvas and were in heat.	Bierbower, 1966

TABLE 5-4 (cont.)

Species/Strain	Sex	No.	Weight/Age	Vehicle	Purity	Dose/Duration	Signs/Symptoms	Reference
Swine/ miniature	M castrated	4	NR/mature	diet	NR	1-2 g/kg bw/day[c] x 3.5-5.5 months	Teats of all animals were maximally enlarged after 2.5 months (development of glandular tissue with secretory material in acini); chronic interstitial renal fibrosis.	Bierbower, 1967a
Swine/ miniature	M castrated	3	NR/11 weeks	diet	NR	2 g/kg bw/day x 18 weeks	Hyperplasia of the ducts in the mammary gland; (changes were less severe than with mature pigs); chronic interstitial renal fibrosis.	Bierbower, 1967b
Swine/ Hormel miniature	M&F	group	25-45 kg/ 8 months	diet	technical grade	1.0 or 2.0 g/kg bw/ day x 6 months or 4.0 g/kg bw/day x 4.5 months	Initial body weight loss in low- and mid-dose groups, then recovery, body weight loss throughout the study in high-dose group; in all groups, dose-dependent breast hyperplasia with milk secretion observed within 7 weeks, none came into estrus; excessively long hair on backs; dose-dependent elevation of BUN; histopathologic examination revealed advanced renal nephritis, (regardless of dose) hyperplastic and hypertrophic mammary glands, hypertrophic uteri, no effect on hematology, no histopathologic changes seen in liver, thyroid, pancreas, adrenals, lungs, heart, stomach, large and small intestine, bladder, prostate, testes, muscle, spleen or bone marrow.	Tegeris et al., 1966
Monkeys/rhesus	NR	NR	NR	intubation: 1% gum tragacanth	NR	0.4, 1.0 or 2.5 g/kg bw/day x 6 months	No effect on body weight or clinical chemistries; no histopathologic tissue damage; normal urinary estrogen pattern, no renal abnormalities; no change in activity of hepatic drug-metabolizing (demethylase activity) enzymes but persistent mitochondrial swelling noted in electron micrographs; decrease in hepatic triglycerides.	Stein, 1970

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TABLE 5-4 (cont.)

Species/Strain	Sex	No.	Weight/Age	Vehicle	Purity	Dose/Duration	Signs/Symptoms	Reference
Humans	M&F	8/group	NR	gelatin capsules	NR	0.5, 1.0 or 2.0 mg/kg bw/day x 4-6 weeks	No effect on clinical chemistry measurements: glucose, blood urea nitrogen, uric acid, total cholesterol, Na, K, total protein, SGOT, SGPT, lactic dehydrogenase, alkaline phosphatase, acid phosphatase; no damage to small intestine, bone marrow, liver or testes as revealed by regular and electron microscopic examination (biopsies 3-6 subjects depending on tissue involved; also from 3 controls); no effect on distribution of fatty acids in subcutaneous fat. No effect on menstrual cycle; in sperm: a shortening of the neck.	Wills, 1969
Humans	M	4/group	NR	by mouth, under supervision	NR	0.5, 1.0 or 2.0 mg/kg bw/day x 6-8 weeks	No effect on body weight or clinical chemistries; no abnormalities seen, under microscopic examination, in biopsies of small intestine, subcutaneous fat, bone marrow, testes or liver, no abnormalities in volume of ejaculate or sperm morphology; no renal abnormalities; electron-microscopy revealed no hepatic changes; no change in percent distribution of fatty acids.	Stein, 1970

[a]Source: Adapted from U.S. EPA, 1983

[b]This group was compared with a pair-fed group, i.e., rats that were given no methoxychlor in a food restricted diet (the same quantity of food consumed by treated rats). The pair-fed control showed similar but slightly less weight reduction, indicating that this effect was due primarily to reduced food consumption.

[c]Two animals were sacrificed after 3.5 months on test diet at 1 g/kg bw/day; the 2 remaining animals were maintained at 1 g/kg bw/day for ~4.5 months, and then given 2 g/kg bw/day for an additional 26 days before sacrifice.

NR = Not reported

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These results indicated that at 10,000 mg/kg diet levels of methoxychlor, another factor, in addition to reduced food consumption, contributed to the reduction in body weight gain. At lower dietary levels, the reduced body weight gain appeared to be dependent only upon reduced food consumption.

Oral studies of 1.5-2 years duration in rats, mice, dogs and swine are summarized in Table 5-5. Inspection of Table 5-5 indicates that long-term feeding of methoxychlor to rats and mice results only in reduced body weight gain (NCI, 1978, Nelson and Fitzhugh, 1951; Hodge et al., 1952; Deichmann et al., 1967). High daily doses of methoxychlor in dogs resulted in some clinical signs of liver damage and behavioral changes (Stein, 1968). High daily doses in swine resulted in loss of body weight, some estrogenic effects and increased BUN (Stein, 1968).

Limited information is available on the effects of subchronic dermal exposure to methoxychlor and results are questionable because of possible vehicle effects. A 90-day LD_{50} in rabbits was estimated to be 600 mg/kg bw/day (Lehman, 1952, 1954). Nelson (1942), as reported by Reuber (1980), described dose-related increased severity of atrophy of the testes and lesions of other organs (bone marrow, liver, kidney, spleen) of 30% methoxychlor in dimethyl phthalate applied to the skin of rabbits 5 days/week for 109 days. The doses ranged from 0.5-4.0 mL/kg bw/day. Information regarding vehicle treated controls was not reported. Haag et al. (1950) described dose related increased severity of fatty degeneration of the liver and brain lesions in rabbits treated with 30% methoxychlor in dimethyl phthalate 5 days/week for 91 days at doses of 0.25-3.0 mL/kg bw/day. The effect of dimethyl phthalate vehicle was reported to be without "apparent ill effect."

TABLE 5-5

Chronic Oral Toxicity of Methoxychlor[a]

Species	Dose	Effect	Reference
Rats, 50 male, Osborne-Mendel (for histopathology n=19-50)	360 mg/kg diet technical grade methoxychlor (95% purity) in corn oil for 29 weeks; then 500 mg/kg diet for 49 weeks[b] (TWA 449 mg/kg diet)	Dose-related depression of body weight gain during treatment; no effect on mortality; no treatment-related histopathological effects in lung, liver, pancreas, kidney, or hematopoietic, endocrine, reproductive, musculoskeletal, circulatory or nervous systems	NCI, 1978
Rats, 50 male, Osborne-Mendel (for histopathology n=18-50)	720 mg/kg diet technical grade methoxychlor in corn oil for 29 weeks; then 1000 mg/kg diet for 29 weeks, then 1000 mg/kg diet cyclically[c] for 29 weeks[b] (TWA 845 mg/kg diet)	Dose-related depression of body weight gains during treatment; no effect on mortality; no treatment related histopathological effects in lung, liver, pancreas, kidney, or hematopoietic, endocrine, reproductive, musculoskeletal, circulatory or nervous systems	NCI, 1978
Rats, 50 female, Osborne-Mendel (for histopathology n=31-50)	750 mg/kg diet technical grade methoxychlor in corn oil for 78 weeks[b] (TWA 750 mg/kg diet)	Dose-related depression of body weight gain during treatment; no effect on mortality; no treatment related histopathological effects in lung, liver, pancreas, kidney, or hematopoietic, endocrine, reproductive, musculoskeletal, circulatory or nervous systems	NCI, 1978
Rats, 50 female, Osborne-Mendel (for histopathology n=30-50)	1500 mg/kg diet technical grade methoxychlor in corn oil for 55 weeks; then 1500 mg/kg diet cyclically for 17 weeks[b] (TWA 1385 mg/kg diet;	Dose-related depression of body weight gain during treatment; no effect on mortality; no treatment related histopathological effects in lung, liver, pancreas, kidney or hematopoietic, endocrine, reproductive, musculoskeletal, circulatory or nervous systems	NCI, 1978

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Species	Dose	Effect	Reference
Rats, Osborne-Mendel, n=24	0, 10, 25, 100, 500 and 2000 mg/kg diet technical methoxychlor in corn oil for 2 years	"Mild stunting" of 2000 mg/kg diet group	Nelson and Fitzhugh, 1951
Rats, 30 male, 30 female, Osborne-Mendel	80 mg/kg diet methoxychlor for 2 years	No effect on longevity, mortality, food consumption, weight gain; primary pathology: chronic murine pneumonitis, testicular tumor in one male rat	Radomski et al., 1965
Weanling rats, 25 male, 25 female	0, 25, 200 and 1600 mg/kg diet methoxychlor for 2 years	Growth retardation at 1600 mg/kg; no dose-related effect on survival time; normal values for urinary sugar and protein; normal red blood cell count, hemoglobin, white blood cell count, differential count; no histological changes in heart, lungs, spleen, stomach, intestines, adrenals, kidneys, testes, bladder, bone marrow, brain; no gross pathology or weight variation with dosage in liver, kidneys, lungs, heart, brain, spleen, stomach and testes	Hodge et al., 1952
Weanling rats, 30 male, 30 female, Osborne-Mendel	0 and 1000 mg/kg diet recrystallized methoxychlor for 27 months	Depression of body weight gain in female rats; normal hematocrit, hemoglobin, erythrocyte, and total and differential leucocyte counts; no effect of treatment in histology of heart, brain, pituitary, pancreas, stomach, small intestine, testes, and ovaries; mean liver weight of females less than control, liver-to-body weight ratio unchanged; histopathology: hydropic swelling, granular cytoplasms, slight fatty metamorphosis, small focal areas of centrolobular necrosis, and passive congestions in liver; very slight infiltration of lymphocytes into renal cortex, and very slight congestion in tubules	Deichmann et al., 1967

TABLE 5-5 (cont.)

Species	Dose	Effect	Reference
Weanling rats, 7 male, 7 female	0, 300, 600, 900, 1200, 2500, 5000 and 10,000 mg/kg diet for 52 weeks	Early mortality occurred in females in the 10,000 mg/kg/ group; growth retardation was observed at ≥2500 mg/kg diet; no histopathology was observed	Haag et al., 1950
Mice, male, B6C3F1, n=50 (for histopathology n=11-47)	1400 mg/kg diet technical grade methoxychlor (95% purity) in corn oil for 1 week; then 1750 mg/kg diet for 77 weeks[d] (TWA 1746 mg/kg diet)	No retardations of weight gains; no effect on mortality; no histopathological effect in lungs, liver, and hematopoietic, circulatory and reproductive systems	NCI, 1978
Mice, male, B6C3F1, n=50 (for histopathology n=11-47)	2800 mg/kg diet technical grade methoxychlor (95% purity) in corn oil for 1 week; then 3500 mg/kg diet for 77 weeks[d] (TWA 3491 mg/kg diet)	Slightly less body weight gain; no effect on mortality; no histopathological effect in lungs, liver, kidney, and hematopoietic, circulatory and reproductive systems	NCI, 1978
Mice, female, B6C3F1, n=50 (for histopathology n=13-50)	750 mg/kg diet technical grade methoxychlor (95% purity) in corn oil for 1 week; then 1000 mg/kg diet for 77 weeks[d] (TWA 1994 mg/kg diet)	Body weight depression; no effect on mortality; no histopathological effect in lungs, liver, kidney, and hematopoietic, circulatory and reproductive systems	NCI, 1978
Mice, female, B6C3F1, n=50 (for histopathology n=13-50)	1500 mg/kg diet technical grade grade methoxychlor (95% purity) in corn oil for 1 week; then 2000 mg/kg diet for 77 weeks[d] (TWA 997 mg/kg diet)	Body weight depression; no effect on mortality; no histopathological effect in lungs, liver, kidney, and hematopoietic, circulatory and reproductive systems	NCI, 1978
Dogs	1000, 2000 and 4000 mg/kg bw/day in diet for 2 years	Loss of body weight; dose dependent increase of SGOT, SGPT and alkaline phosphatase; normal hematology; general loss of subcultaneous fat at necropsy; 2000 and 4000 mg/kg: behavioral change	Stein, 1968

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TABLE 5-5 (cont.)

Species	Dose	Effect	Reference
Dogs, 1 male, 3 female	300 mg/kg bw/day methoxychlor in capsules as 10% solutions in corn oil mixed in diet for 3.5 years	Increased fat in kidney of one dog; small number of hepatic cells with foamy cytoplasm in one dog, which had a hepato-cellular carcinoma; fibrotic areas containing macrophages with yellowish pigment in liver of second dog; small amount of fat in liver; increased lipid in adrenals; chronic cholecystitis in both dogs (early death at 105 and 260 days for male and 1 female dog)	Nelson and Radomski, 1953
Swine	1000 and 2000 mg/kg bw/day in diet for 2 years	Loss of body weight for first 8 weeks; then slow gain in weight	Stein, 1968
Swine	4000 mg/kg bw/day in diet for 2 years	Loss of body weight for first 8 weeks; original weight not regained	Stein, 1968
Swine	1000, 2000 and 4000 mg/kg bw/day in diet for 2 years	Increase of BUN; marked mammary hyperplasia with milk secretion; anestrus; growth of long black hair on back; chronic intersti-tial nephritis, increase of uterine weight	Stein, 1968

[a]Source: Adapted from U.S. EPA, 1983

[b]33-week observation period followed treatment

[c]Cycle: 4 weeks of treatment and 1 week dosage-free treatment

[d]15-week observation period followed treatment

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Limited information regarding subchronic inhalation exposure to methoxychlor is available. Again, the effects of solvents and vehicle compromise the reliability of the results. Haag et al. (1950) mixed micronized dust that contained 10% recrystallized methoxychlor with Pyrax (not further described) and 3% Santo-Cel (dehydrated silica gel) and exposed dogs, rabbits and rats to inhalations of the mixture. Increased mortality and reduced body weight gain were partially attributed to Santo-Cel and to the diluent Pyrax. Haag et al. (1950) exposed 10 rats and 2 dogs to inhalations of methoxychlor in kerosene. Results were confounded by the toxicity of kerosene to control animals.

5.6. OTHER RELEVANT INFORMATION

The acute oral LD_{50} of methoxychlor in lipid vehicle, either technical grade or purified, was reported to be ~6 g/kg bw in rats (Hodge et al., 1950; Smith et al., 1946; Lehman, 1951). Acute oral LD_{50}s in other species were reported to be >2.0 g/kg bw in hamsters (Cabral et al., 1979), >2.5 g/kg bw in monkeys and 2.9 g/kg bw in mice (Coulston and Serrone, 1969). Signs of toxicity following acute oral exposure in rats included CNS depression, weakness, diarrhea and death within 36-48 hours (Smith et al., 1946; Lehman, 1951). Histopathological changes in liver, gall bladder, heart and kidney were observed in rabbits treated by gavage with 200 mg methoxychlor/kg bw/day (Smith et al., 1946; Lillie et al., 1947). The rabbits died after 4-15 daily doses. Rats receiving relatively low single oral doses of methoxychlor (0.04-0.64 g/kg bw) had altered glycogen metabolism in the liver (Morgan and Hickenbottom, 1979). The changes included decreased lactate content and phosphorylase activity and increased glucose-6-phosphatase activity.

Methoxychlor has been shown to affect microsomal enzyme levels. Rats treated orally by gavage with ~300-1200 mg/kg bw/day for 3 days had decreased hexobarbital sleeping time, increased amidopyrine-N-demethylase activity and increased ascorbic acid content in urine (Klinger et al., 1973). Rats treated with a single dose of methoxychlor in dioxane at 500 mg/kg bw by gavage had increased activity of hepatic (slight) and intestinal (2-fold) aryl hydrocarbon hydroxylase compared with controls (Manis and Kim, 1980). Intraperitoneal injection of 100 mg methoxychlor/kg bw for 3 days in rats resulted in stimulation of N-dealkylation of aminopyrine by liver microsomes (Hart and Fouts, 1965). Mice treated intraperitoneally with 99% pure methoxychlor at 100 mg/kg bw/day for 5 days had significantly elevated p-chlorothioanisole sulfoxidation activity and significantly decreased N-dimethylase activity and cytochrome P-450 content in hepatic microsomes (Nigg et al., 1976).

Lamartiniere et al. (1982) reported that when neonatal rats were treated subcutaneously with 98% pure methoxychlor at 3 mg/rat/day on days 2, 4 and 6 postpartum, the activity of hepatic monoamine oxidase (a sex-differentiated enzyme) was significantly ($p<0.01$) increased in both males and females when they were adults (63 days) but not when they were prepubertal (20 days). When male rats were treated, either as adults or prepubertally, with equivalent doses (3x333 mg/kg bw), there was no effect on the enzyme activity. Methoxychlor may have bound to the hypothalamic estrogen receptor when administered during the critical period of rat development, thereby altering the sex-differentiation of the enzyme.

6. AQUATIC TOXICITY

6.1. ACUTE

Acute toxicity information is available for at least 27 freshwater invertebrates, 20 freshwater fishes, 6 marine invertebrates and 9 marine fishes (Table 6-1). The acute LC_{50} ranged from 0.5-63 µg/ℓ for freshwater invertebrates and from 7.5-230 µg/ℓ for freshwater fishes. A similar range of acute LC_{50} values has been reported for marine animals ranging from 3.5-300 µg/ℓ for invertebrates and from 3.5-150 µg/ℓ for fishes. Of the 62 tested aquatic animal species, all but 5 had LC_{50} values <100 µg/ℓ.

Johnson and Finley (1980) summarized the results of several investigations concerning the effects of temperature, pH and water hardness on the acute toxicity of methoxychlor to freshwater animals. Temperature variation from 15-21°C had no effect on the toxicity to daphnids, but increased temperature resulted in a slightly lower toxicity to rainbow trout and bluegills. Acute toxicity to brook trout did not vary within a pH range of 6.5-8.5. Similarly, toxicity did not vary for cutthroat trout, brook trout and bluegill at water hardness levels ranging from 42-300 mg/ℓ.

Another factor that has been shown to affect the apparent acute toxicity of methoxychlor is the type of pesticide formulation. Sebastien and Lockhart (1981) reported that an emulsifiable formulation was more acutely toxic than a particulate formulation to midge larvae, stonefly larvae and fish. Both formulations were equally toxic to blackfly larvae. The equal toxicity with blackflies was probably related to the fact that only blackflies among the species tested are filter feeders.

TABLE 6-1

Acute Toxicity of Methoxychlor to Aquatic Animals

Species	Method	LC_{50} (µg/ℓ)	Reference
FRESHWATER ORGANISMS			
Blackfly *Simulium damnosum*	S, U	25	Thompson, 1975
Mosquito *Aedes aegypti*	S, U	83	Ginsburg, 1947a,b
Mosquito *Aedes aegypti*	S, U	23.3	Burchfield and Storrs, 1954
Mosquito *Aedes cantans*	S, U	31.5	Rettich, 1977
Mosquito *Aedes punctor*	S, U	63.1	Rettich, 1977
Mosquito *Culex pipiens pipiens*	S, U	8.9	Rettich, 1977
Mosquito *Culex pipiens molestus*	S, U	18.9	Rettich, 1977
Mosquito *Caliseta annulata*	S, U	38.3	Rettich, 1977
Midge *Chironomus tentans*	FT, U	1.62	Merna and Eisele, 1973
Midge *Chironomus tentans*	FT, M	1.49	Bender and Eisele, 1971
Mayfly *Stenonema interpunctatus*	FT, U	1.96	Merna and Eisele, 1973
Mayfly *Stenonema candidum*	FT, M	1.83	Bender and Eisele, 1971
Mayfly *Stenonema* sp.	FT, M	1.27	Bender and Eisele, 1971

TABLE 6-1 (cont.)

Species	Method	LC_{50} (µg/ℓ)	Reference
Mayfly *Stenonema* sp.	FT, U	0.63	Bender and Eisele, 1971
Caddis fly *Cheumatopsche* sp.	FT, U	3.24	Merna and Eisele, 1973
Stonefly *Pteronarcys californica*	S, U	8	Sanders and Cope, 1966
Stonefly *Pteronarcys californica*	S, U	1.4	Cope, 1965
Stonefly *Pteronarcys californica*	S, U	1.4	Johnson and Finley, 1980
Stonefly *Pteronarcella badia*	S, U	10	Johnson and Finley, 1980
Stonefly *Taenropteryx nivalis*	FT, U	0.98	Bender and Eisele, 1971
Cladoceran *Daphnia magna*	S, U	3.6	Anderson, 1959
Cladoceran *Daphnia magna*	S, U	3.7	Frear and Boyd, 1967
Cladoceran *Daphnia magna*	S, U	6	Knapek and Lakota, 1974
Cladoceran *Daphnia magna*	S, U	0.8	FWPCA, 1968
Cladoceran *Daphnia pulex*	S, U	0.78	Sanders and Cope, 1966
Cladoceran *Simocephalus serrulatus*	S, U	5.0	Sanders and Cope, 1966

TABLE 6-1 (cont.)

Species	Method	LC_{50} (µg/ℓ)	Reference
Cladoceran *Simocephalus serrulatus*	S, U	5.6	Sanders and Cope, 1966
Scud *Gammarus lacustris*	S, U	0.8	Sanders, 1969
Scud *Gammarus lacustris*	S, U	1.3	FWPCA, 1968
Scud *Gammarus pseudolimnaeus*	FT, U	1.14	Merna and Eisele, 1973
Scud *Gammarus pseudolimnaeus*	FT, U	0.75	Merna and Eisele, 1973
Scud *Gammarus fasciatus*	S, U	1.9	Johnson and Finley, 1980
Ostracod *Cypridopsis vidua*	S, U	32	Johnson and Finley, 1980
Isopod *Asellus brevicaudus*	S, U	34	Johnson and Finley, 1980
Isopod *Asellus communis*	FT, M	1.78	Anderson and DeFoe, 1980
Crayfish *Orconectes virilis*	FT, U	2.15	Merna and Eisele, 1973
Crayfish *Orconectes virilis*	FT, M	7.05	Eisele, 1975
Crayfish *Orconectes nais*	S, U	0.50	Johnson and Finley, 1980
Glass shrimp *Palaemonetes kadiakensis*	S, U	1.05	Johnson and Finley, 1980
Rainbow trout *Salmo gairdneri*	S, U	62	Johnson and Finley, 1980

TABLE 6-1 (cont.)

Species	Method	LC_{50} (µg/ℓ)	Reference
Rainbow trout *Salmo gairdneri*	S, U	30	Macek et al., 1969
Rainbow trout *Salmo gairdneri*	S, U	62.6	Katz, 1961
Brown trout *Salmo trutta*	S, U	14	Knapek and Lakota, 1974
Brown trout *Salmo trutta*	S, U	14	Lakota, 1974
Cutthroat trout *Salmo clarki*	S, U	15	Johnson and Finley, 1980
Brook trout *Salvelinus fontinalis*	S, U	19	Johnson and Finley, 1980
Lake trout *Salvelinus namaycush*	S, U	17	Johnson and Finley, 1980
Atlantic salmon *Salmo salar*	S, U	16.4	Johnson and Finley, 1980
Coho salmon *Onchorynchus kisutch*	S, U	62.6	Katz, 1961
Chinook salmon *Onchorynchus tshawytscha*	S, U	27.9	Katz, 1961
Guppies *Lebistes reticulatus*	S, U	120	Tarzwell, 1959
Guppies *Lebistes reticulatus*	S, U	230	Lakota, 1974
White sucker *Catostomus commersoni*	FT, U	34.5	Walwood and Johansen, 1974
Northern pike *Esox lucius*	S, U	12	Johnson and Finley, 1980

TABLE 6-1 (cont.)

Species	Method	LC_{50} (µg/ℓ)	Reference
Channel catfish *Ictalurus punctatus*	S, U	52	Johnson and Finley, 1980
Largemouth bass *Micropterus salmoides*	S, U	16	Johnson and Finley, 1980
Yellow perch *Perca flavescens*	S, U	30.0	Johnson and Finley, 1980
Yellow perch *Perca flavescens*	FT, M	30	Merna et al., 1972
Yellow perch *Perca flavescens*	FT, M	20.12	Merna and Eisele, 1973
Tench *Tinca tinca*	S, U	162	Lakota, 1974
Tench *Tinca tinca*	S, U	162	Knapek and Lakota, 1974
Three-spined stickelback *Gasterosteus aculeatus*	S, U	86.4	Katz, 1961
Three-spined stickelback *Gasterosteus aculeatus*	S, U	69.1	Katz, 1961
Fathead minnow *Pimephales promelas*	S, U	64	Tarzwell, 1959
Fathead minnow *Pimephales promelas*	S, U	39	Johnson and Finley, 1980
Fathead minnow *Pimpehales promelas*	S, U	35	Tarzwell, 1959
Fathead minnow *Pimephales promelas*	S, U	7.5	Merna et al., 1972
Fathead minnow *Pimephales promelas*	FT, U	8.54	Merna and Eisele, 1973

TABLE 6-1 (cont.)

Species	Method	LC_{50} (µg/ℓ)	Reference
Carp *Cyprinus carpio*	S, U	56	Knapek and Lakota, 1974
Carp *Cyprinus carpio*	S, U	29	Lakota, 1974
Goldfish *Carassius auratus*	S, U	63	Ginsburg, 1947a,b
Goldfish *Carassius auratus*	S, U	56	Tarzwell, 1959
Goldfish *Carassius auratus*	S, U	42	Johnson and Finley, 1980
Bluegill *Lepomis macrochirus*	S, U	32	Johnson and Finley, 1980
Bluegill *Lepomis macrochirus*	S, U	62	Tarzwell, 1959; Weiss, 1964
Bluegill *Lepomis macrochirus*	S, U	40	Kennedy et al., 1970
Bluegill *Lepomis macrochirus*	S, U	42	Macek et al., 1969
MARINE SPECIES			
Pacific oyster *Crassostrea gigas*	S, U	300	Cardwell et al., 1978
Horse clam *Tresus capax*	S, U	250	Cardwell et al., 1978
Pink shrimp *Penaens duorarum*	S, U	3.5	Bahner and Nimmo, 1975
Sand shrimp *Crangon septemspinosa*	S, U	4	Eisler, 1969

TABLE 6-1 (cont.)

Species	Method	LC_{50} (µg/ℓ)	Reference
Grass shrimp *Palaemonetes vulgaris*	S, U	12	Eisler, 1969
Hermit crab *Pagurus longicarpus*	S, U	7	Eisler, 1969
Mummichog *Fundulus heteroclitus*	S, M	35	Eisler, 1970a
Mummichog *Fundulus heteroclitus*	S, M	35	Eisler, 1970b
Striped killifish *Fundulus majalis*	S, U	30	Eisler, 1970b
American eel *Anguilla nostrata*	S, U	12	Eisler, 1970b
Bluehead *Thalassoma bifasciatum*	S, U	13	Eisler, 1970b
Striped mullet *Mugil cephalus*	S, U	63	Eisler, 1970b
Atlantic silversides *Menidia menidia*	S, U	33	Eisler, 1970b
Northern puffer *Sphaeroides maculatus*	S, U	150	Eisler, 1970b
Striped bass *Morone saxatilis*	S, U	3.3	Korn and Earnest, 1974
Sheepshead minnow *Cyprinodon variegatus*	FT, M	49	Parrish et al., 1977

S = Static; FT = Flowthrough; M = Measured concentrations; U = Unmeasured concentrations

6.2. CHRONIC

Chronic toxicity data are available for at least eight freshwater invertebrates, three freshwater fishes, two marine invertebrates and one marine fish species (Table 6-2). Chronic exposure for up to 42 days resulted in LC_{50} values ranging from 0.21-1.30 µg/ℓ for five freshwater arthropods, but two other species (stoneflies and snails) were not affected by 28 days of exposure to 4.2 µg/ℓ. Chronically toxic methoxychlor concentrations ranged from 0.625-23 µg/ℓ for freshwater and marine fish species and from 0.05-62 µg/ℓ for marine invertebrates. The most sensitive species was the Dungeness crab, which showed increased mortality and delayed molting of larvae at 0.05 µg/ℓ.

6.3. PLANT EFFECTS

The available data concerning the effects of methoxychlor on aquatic plants are summarized in Table 6-3. The lowest reported toxic concentration is 100 µg/ℓ, which inhibited the growth of freshwater algae, Chlorella pyrenoidosa (Kricher et al., 1975) and three of five species of marine algae (Sikka and Rice, 1974). Exposure of mixed algae cultures to methoxychlor caused reduced ^{14}C uptake at 1000 µg/ℓ (Butler, 1963) but not at 100 µg/ℓ (Page and Colman, 1976). Other data indicate that methoxychlor may be stimulatory to some algae at concentrations ranging from 20 µg/ℓ (Wurtzbaugh and Apperson, 1978) to 100 mg/ℓ (Poorman, 1973). The available data indicate that aquatic plants are less sensitive than most aquatic animals to methoxychlor.

6.4. RESIDUES

Numerous investigations have been conducted to determine the ambient levels of methoxychlor in aquatic organisms. The levels of methoxychlor in edible aquatic organisms were given in Table 3-2. The data indicate that

TABLE 6-2

Chronic Effects of Methoxychlor on Aquatic Animals

Species	Duration (days)	Highest Nontoxic Concentration (µg/l)	Lowest Toxic Concentration (µg/l)	Toxic Effect	Reference
		FRESHWATER			
INVERTEBRATES					
Isopod Asellus communis	28	NR	0.42	LC_{50}	Anderson and Defoe, 1980
Amphipod Gammarus pseudolimnaeus	42	NR	0.22	LC_{50}	Merna and Eisele, 1973
Mayfly Stenonema terminatum	14 28	NR 0.25	0.41 0.5	LC_{50} emergence	Merna and Eisele, 1973 Merna and Eisele, 1973
Mayfly Stenonema interpunctatum	28	NR	0.22	LC_{50}	Merna and Eisele, 1973
Caddisfly Hydropsyche sp.	28	NR	1.30	LC_{50}	Anderson and Defoe, 1980
Caddisfly Cheumatopsyche sp.	42	NR	0.21	LC_{50}	Merna and Eisele, 1973
Stonefly Pteronarcys dorsata	28	4.20	NR	no mortality	Anderson and Defoe, 1980
Snail Physa integra	28	4.20	NR	no mortality	Anderson and Defoe, 1980
FISH					
Yellow perch Perca flavescens	210	NR	0.625	growth inhibition	Merna and Eisele, 1973
Fathead minnow Pimephales promelas	180	1.0	2.0	reproductive inhibition	Merna and Eisele, 1973
Bluegill Lepomis macrochirus	84	NR	10	reversible histopathology	Kennedy et al., 1970

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TABLE 6-2 (cont.)

Species	Duration (days)	Highest Nontoxic Concentration (µg/l)	Lowest Toxic Concentration (µg/l)	Toxic Effect	Reference
		SALTWATER			
INVERTEBRATES					
Dungeness crab *Cancer magister*	60	0.005	0.05	increased mortality, delayed molting	Armstrong et al., 1976
Mussel *Mytilus edulis*	20	31	62	decreased growth and survival	Liu and Lee, 1975
FISH					
Sheepshead minnow *Cyprinodon variegatus*	140	12	23	decreased hatching	Hansen and Parrish, 1977

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TABLE 6-3

Effects of Methoxychlor on Aquatic Plants

Species	Duration	Concentration (µg/ℓ)	Effect	Reference
FRESHWATER				
Mixed algae (at least 11 species)	4 hours	100	no effect on ^{14}C uptake	Page and Colman, 1976
Chlorella pyrenoidosa	164 hours	100	17% growth inhibition	Kricher et al., 1975
Algae (36 isolates of 8 species)	2 weeks	10	no effects on growth	Butler et al., 1975
Mixed algae	6 days	20	increased N_2 fixation	Wurtzbaugh and Apperson, 1978
Euglena gracilis	1 week	10,000-100,000	growth stimulation	Poorman, 1973
SALTWATER				
Algae (5 species)	5 days	100	inhibitory to 3 species no effect on 2 species	Sikka and Rice, 1974
Mixed algae	4 hours	1000	reduced CO_2 uptake	Butler, 1963
Macrophytic algae (3 species)	1-3 weeks	23	no effect on growth	Sikka et al., 1976

methoxychlor is rarely detectable in edible aquatic organisms, even in those sampled from areas that have been treated with this pesticide. As was shown in Table 3-2, the highest residue levels (0.23-1.75 ppm) were reported in rainbow trout shortly after treatment of a river with methoxychlor for blackfly control (Lockhart et al., 1977).

In contrast to these studies of ambient methoxychlor residues, numerous other studies have shown that methoxychlor can bioconcentrate in aquatic organisms experimentally exposed to elevated pesticide levels several orders of magnitude above the residue levels found in ambient water (see Table 3-1). Equilibrium BCFs were 8300 for fathead minnows (Veith et al., 1979), 113-264 for sheepshead minnows (Hansen and Parrish, 1977), 350-1150 for stoneflies (Anderson and Defoe, 1980) and 5000-8600 for snails (Anderson and Defoe, 1980). Although these and many other studies indicate that methoxychlor can bioconcentrate to high levels, the general absence of methoxychlor residues even in treated areas is probably due in part to its fairly rapid elimination once exposure has ended. Experimental studies have shown that >90% of accumulated methoxychlor is eliminated within 1-2 weeks by fish and invertebrates (Reinbold et al., 1971; Butler, 1971; Armstrong et al., 1976).

6.5. OTHER RELEVANT INFORMATION

Several investigations concerning food chain transfer (or biomagnification) and ecological effects of methoxychlor have been conducted. Model food chain studies (Johnson, 1974; Reinbold et al., 1971) have shown that fish fed contaminated daphnids did not accumulate methoxychlor above the concentration in the food, indicating that biomagnification did not occur. Numerous studies have shown that treatment of streams and rivers with methoxychlor to control blackflies results in serious mortalities among nontarget species (Jamnback and Frempong-Boadu, 1966; Fredeen, 1974, 1975;

Flannagan et al., 1979). Even if acute toxic effects are absent in such treatments, it is still possible that subtle effects on species composition may occur. For instance, treatment of ponds with 10-40 µg/ℓ resulted in an overall increase in the number of benthic invertebrates, which was due in part to an increase of midge larvae populations (Kennedy et al., 1970).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

An ADI for humans of 0.1 mg methoxychlor/kg bw/day was recommended by NAS (1977). This ADI was based on a NOAEL for rats of 10 mg/kg bw/day derived from the study of Haag et al. (1950). The temporary ADI of methoxychlor for humans, established by the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Residues (WHO, 1975) and confirmed in 1977 (FAO/WHO, 1978) was 0-0.1 mg/kg bw.

An interim standard for the maximum contaminant level of 0.1 mg/ℓ for methoxychlor in drinking water was promulgated by the U.S. EPA in 1975 (Federal Register, 1975). The FDA established the same value for maximum contaminant level for bottled water (Federal Register, 1984). A NOAEL for methoxychlor in drinking water of 0.700 mg/ℓ, assuming 20% of the ADI is consumed in drinking water, or 0.035 mg/ℓ, assuming that 100% of the ADI comes from this source, was suggested by NAS (1977).

The following tolerances established by the U.S. EPA for methoxychlor residues in or on raw agricultural commodities are as follows: forage crops, 100 ppm; various fruits and vegetables, 14 ppm; sweet potatoes and yams from pre- and postharvest application, 7 ppm; meat fat, 3 ppm; grains from treatment in storage, 2 ppm; milk fat (which reflects negligible residues in milk), 1.25 ppm; potatoes, 1 ppm and horseradish, 1 ppm (Code of Federal Regulations, 1980).

The TLV for methoxychlor in workplace air of 10 mg/m³ as a TWA for an 8-hour workday was adopted by the ACGIH (1983). This value was based on reports of Lehman (1952), Hodge et al. (1952) and Tegeris et al. (1966)

that methoxychlor is of a low order of oral toxicity to animals and was considered to be sufficiently low to protect against a health hazard to humans (ACGIH, 1980). A TWA for methoxychlor in the workplace was established by OSHA (1981) as 15 mg/m³.

7.2. AQUATIC

Existing guidelines and standards for the protection of nontarget aquatic organisms from the effects of methoxychlor were not located in the available literature.

8. RISK ASSESSMENT

Methoxychlor has been studied for its carcinogenic potential in a number of chronic dietary studies in rats (Radomski et al., 1965; Deichmann et al., 1967; Nelson and Fitzhugh, 1951; Hodge et al., 1952; NCI, 1978) mice (NCI, 1978; Davis, 1969) and dogs (Nelson and Radomski, 1953). Methoxychlor has also been tested as a carcinogen in chronic dermal application and subcutaneous injection in mice (Hodge et al., 1966). In none of these studies, in which the highest dietary levels were 2000 mg/kg diet in rats (Nelson and Fitzhugh, 1951), 3491 mg/kg diet (TWA) in mice (NCI, 1978) and a dose of 300 mg/kg bw/day in dogs (Nelson and Radomski, 1953), did the investigators find a treatment-related increase in tumor incidence at any site. A re-evaluation of the histological slides from these studies by Reuber (1978, 1979a,b, 1980) indicated that methoxychlor had a positive carcinogenic effect in rats and mice; however, the conclusions of NCI (1978), IARC (1979) and U.S. EPA (1983) supported the findings of the original investigators that methoxychlor was not carcinogenic under the conditions of the studies.

Negative responses were found for methoxychlor in a number of mutagenicity assays, with and without metabolic activation, in all strains of *S. typhimurium* and *E. coli* for reverse mutation (Probst et al., 1981; Simmon, 1979; Waters et al., 1982; Grant et al., 1976; Wildeman and Nazar, 1982; Ashwood-Smith et al., 1972). Methoxychlor was negative for DNA damage induced recombinations in the yeast *S. cerevisiae* (Waters et al., 1982), sex linked recessive mutation in *D. melanogaster* (Waters et al., 1982; Benes and Sram, 1969) and transformation and unscheduled DNA synthesis in cultured mammalian cell systems (Dunkel et al., 1981; Probst et al., 1981; Waters et al., 1982). Positive responses were obtained for forward mutation and cell

transformation in cultured mouse cell systems (Myhr et al., 1981; Dunkel et al., 1981). Evidence was presented that daily gavage doses of 200 and 400 mg/kg bw of technical grade methoxychlor to pregnant rats on days 6-15 of gestation resulted in fetotoxicity (i.e., reduced number of live fetuses, reduced fetal body weight) (Khera et al., 1978). The incidence of wavy ribs was significantly increased over controls at doses of $\geq$100 mg/kg bw.

No effect on reproductive performance was observed in female rats treated with 1000 mg methoxychlor/kg diet throughout pregnancy and lactation, although early vaginal opening and decreased reproductive performance were observed in the offspring (Harris et al., 1974). Subchronic exposure to high dietary levels of methoxychlor in rats (10,000 mg/kg diet) and swine (1-4 g/kg bw/day) resulted in effects on reproductive organs (Tullner and Edgcomb, 1962; Hodge et al., 1950; Bierbower, 1966, 1967a,b; Tegeris et al., 1966).

Since the data indicate that methoxychlor was not an animal carcinogen, it is appropriate to derive an ADI for methoxychlor based on toxicity. Data from human experience with exposure to methoxychlor are insufficient to derive an ADI. Wills (1969) reported that oral administration of 0.5-2.0 mg/kg bw/day for 4-6 weeks to human volunteers resulted in shortened necks of spermatozoa; however, insufficient detail was provided to evaluate this effect, which was reported only during a question and answer period at the end of the paper. Data from studies of chronic dietary exposure of laboratory animals can be used to determine a NOAEL to estimate an ADI. Data from other chronic and subchronic exposure studies support the chronic data.

In the NCI (1978) bioassay, Osborne-Mendel rats and B6C3F_1 mice were maintained on diets containing methoxychlor for 78 weeks. The rats and mice were observed for an additional 33 and 15 weeks, respectively. Treated

groups consisted of 50 male and 50 female animals. Control groups consisted of 20 animals of each sex. The TWA high and low concentrations of methoxychlor were 845 and 448 mg/kg diet for male rats, 1385 and 750 mg/kg diet for female rats, 3491 and 1746 mg/kg diet for male mice and 1994 and 997 mg/kg diet for female mice. Comprehensive histological examination of necropsied animals was performed. The only treatment-related effect observed was a dose-related decrease in body weight gain. Whether the decrease was significant was not clear. When treatment was terminated, the treated animals gained weight comparable with controls. In studies of shorter-term duration using pair-fed control rats, it was demonstrated that reduced body weight gain was due to refusal of food, as well as some other factor, particularly at high dietary levels (10,000 mg/kg diet) (Hodge et al., 1950; Tullner and Edgcomb, 1962; Davison and Cox, 1976).

In an earlier chronic toxicity study, groups of 25 male and 25 female rats were maintained on diets containing methoxychlor in concentrations of 0, 25, 200 or 1600 mg/kg diet for 2 years (Hodge et al., 1952). Growth retardation was observed in the high-dose group, while no adverse effects were found at the two lower dietary levels. Clinical hematology and urinalysis revealed no abnormalities. The 1600 mg/kg diet may represent a NOAEL for lifetime methoxychlor exposure, since reduced body weight gain probably reflected an organoleptic rather than a toxic effect. In another study, however, groups of 30 male and 30 female Osborne-Mendel rats maintained on a diet containing 1000 mg methoxychlor/kg diet for 27 months had histologic changes in the liver such as hydropic swelling, granular cytoplasm, fatty changes, focal centrilobular necrosis and congestion (Deichmann et al., 1967). The details of the histologic findings in treated and control rats were not compared; however, lungs, kidneys, spleen and "other organs and tissues were essentially normal."

Decreased testicular weight was observed in rats (12 male rats per group) fed dietary levels of methoxychlor of 2000 mg/kg bw for 90 days (Shain et al., 1977). Therefore, the 1000 mg/kg diet level resulting in hepatic lesions (Deichmann et al., 1967) represents a LOAEL. The highest dietary level at which no systemic toxic effects were observed below this LOAEL in all available studies, and representing a NOAEL for lifetime methoxychlor exposure, is the TWA concentration of 750 mg/kg diet resulting in reduced body weight gain in female rats (NCI, 1978).

Using an uncertainty factor of 100 for an animal NOAEL and the 750 mg/kg diet level (37.5 mg/kg bw/day, assuming a rat consumes an amount of food/day equal to 5% of its body weight), the ADI for methoxychlor by humans can be calculated, assuming that an average human weighs 70 kg: ADI = 750 mg/kg diet x 0.05 x 70 kg ÷ 100 = 26.25 mg/human/day. The ADI is equivalent to 0.375 mg/kg bw/day.

It is difficult to assess the ADI of 0.1 mg/kg/day proposed by NAS (1977). In the text, the study used for derivation is cited as Haag et al. (1950); however, this reference does not report data similar to the study cited by NAS. In the subsequent table, the study used for ADI derivation is cited as Haag et al. (1959); however, there is no corresponding citation in the reference section. In addition, the NCI (1978) study was published subsequent to the NAS (1977) report and establishes a higher NOAEL, which is consistent with other published data in that it is below other reported LOAELs.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence.

These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal studies that indicate that a more conservative ADI should be adopted. Based upon a NOAEL of 10 mg/kg bw/day (from rats fed 200 ppm diet during gestation), a human ADI of 0.1 mg/kg bw/day, or 7 mg/day for a 70 kg adult, is derived. An uncertainty factor of 100 (10 to account for interspecies extrapolation and 10 for protection of the most sensitive individuals within the human population) was used in this calculation. The same 200 ppm dietary level further represented a NOEL for fetotoxicity and a NOEL for reproductive performance in other rat studies.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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Many of the summary tables and portions of Sections 2 and 3 of this profile were adapted from the following document:

Smith, N.J., D.A. Gray, J. Colman, et al. 1981. Criteria Document for Methoxychlor. Final draft. Prepared by Syracuse Research Corporation under Contract 63-03-2892 for ECAO, U.S. EPA, Cincinnati, OH.